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Review

A disease state approach to the pharmacological management of Type 2 diabetes in primary care: A position statement by Primary Care Diabetes Europe

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ABSTRACT

Type 2 diabetes and its associated comorbidities are growing more prevalent, and the complexity of optimising glycaemic control is increasing, especially on the frontlines of patient care. In many countries, most patients with type 2 diabetes are managed in a primary care setting. However, primary healthcare professionals face the challenge of the growing plethora of available treatment options for managing hyperglycaemia, leading to difficultly in making treatment decisions and contributing to therapeutic inertia. This position statement offers a simple and patient-centred clinical decision-making model with practical treatment recommendations that can be widely implemented by primary care clinicians worldwide through shared-decision conversations with their patients. It highlights the importance of managing cardiovascular disease and elevated cardiovascular risk in people with type 2 diabetes and aims to provide innovative risk stratification and treatment strategies that connect patients with the most effective care.

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1. Statement of intent

New and emerging medical therapies and evidence have changed the landscape for managing people with type 2 diabetes (T2D) with established cardiovascular disease (CVD) and those with cardiovascular risk factors. Previously, guidelines gauged good diabetes care primarily based on glycated haemoglobin (HbA_{1c}) targets [1], but recent updates have represented a major shift in recommendations. Effective glycaemic control also remains an important consideration for prevention or improvement of microvascular disease. The reality of primary care necessitates an increasingly holistic and integrated care approach for optimal patient management [2,3].

This position statement, written by primary care practitioners and for primary care practitioners, supports a comprehensive disease state approach to clinical decision making in management of patients with T2D. It is intended to provide a simple and effective guide to evaluate cardiovascular risk in people with T2D managed in primary care, and clear and practical treatment recommendations that can be useful for healthcare professionals (HCPs) globally who manage people with diabetes in a primary care setting. The role of primary care physicians as frontline clinicians in chronic disease management varies worldwide. While every country will have its own treatment realities, this position statement aims to provide a critical interpretation of the best available evidence and a unique tool to facilitate its application in primary care clinical decision making. The guiding scientific principles will be applied differently, contingent on treatment access and the financial or economic limitations of patients and their country-specific healthcare systems [4,5].

2. Introduction and rationale

The severe burden of T2D is recognised globally [6], accounting for approximately 90% of the 425 million estimated diabetes cases worldwide [5]. Diabetes can be successfully managed, and its associated complications prevented, especially if detected and treated early [7]. Understanding the complexity of the disease and the pharmacological options is critical for ensuring optimal patient care and improving outcomes.

When not treated in a timely and effective manner, poorly managed T2D is associated with life-threatening complications, including chronic kidney disease (CKD), amputations, blindness and CVD [8,9]. The presence of multimorbidity is the reality for the vast majority of patients with T2D. CVD affects about 30% of all people with T2D [10] and is a major cause of morbidity and mortality [5]. Thus, a comprehensive diabetes management plan for both the primary and secondary prevention of CVD is important for educating patients to make informed decisions that will help them succeed in reaching their glycaemic target goals and prevent the number and complexity of serious complications [11,12].

As experts in 'whole-person medicine', primary care physicians are tasked with using their generalist expertise to work with their patients to develop a comprehensive treatment plan that addresses all of their health needs and goals. Indeed, an evidence-based generalist approach has been suggested as the way forward to address the complex challenges of multimorbidity and avoid the pitfalls of treating each disease state in isolation [13]. Access to patient-centred care can significantly improve outcomes for people with T2D, and this process begins at the level of primary care. The majority of routine T2D management occurs in primary care [14], as part of the chronic care model which focuses on a multidisciplinary team approach involving specialists, dieticians, nurses and other allied HCPs [2,15,16]. While nurses play a central role in primary care, their degree of professional involvement and utilisation can vary widely across different healthcare systems [17,18]. Nonetheless, patients continue to benefit from treatment models anchored in primary care, as general practitioners are able to provide timely and informed treatment recommendations based on their clinical expertise in chronic disease management and an effective patient–physician relationship enabled by continuity of

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care [19]. Primary care physicians are uniquely placed to adopt shared decision-making models of care, where HCPs and patients co-develop treatment goals through dialogue and with reference to the benefits and risks of different treatment options [11,12,15]. These conversations should also address treatment access, drug cost, reimbursement options and local prescribing guidelines.

In spite of this, an increasing number of HCPs struggle with therapeutic inertia when treating diabetes [20–22]. Moreover, there is room for improvement in the control of risk factors in T2D patients worldwide [23,24]. The clinical decision process in primary care is exceedingly complex, and some primary care practitioners struggle to maintain up to date knowledge in a changing scientific landscape and with limited resources available to care for their patients. Research identifies a lack of adherence to treatment guidelines among these challenges, resulting in delayed or inappropriate therapy advancement [25] and failure to meet guideline-recommended targets [26]. Patients often lack clear and personalised healthcare agendas because of clinicians' concerns related to medication issues, the complexity of creating tailored treatment plans for patients with multimorbidity, and in some instances, budget constraints. Patients also struggle with adherence to medication regimens, particularly when treated with multiple agents [27]. Despite these challenges, high-quality diabetes care has been shown to be achievable in the primary care setting [28,29]. As such, training in optimal use of available therapies and primary care-specific treatment guidelines are necessary to overcome therapeutic inertia, improve T2D control and prevent complications.

The paucity of randomised controlled trials (RCTs) carried out in primary care populations has served as a potential barrier for the development of treatment guidelines and tools specific for primary care [30]. Even though there has been an increase in the proportion of diabetes research outputs from primary care in recent years, this still lags significantly behind the total research output in diabetes (0.5% in 1996 and 2.2% in 2016) [31].

Moreover, the full patient population treated in primary care often differs widely from those who meet the inclusion criteria of clinical trials, with the general population typically being older and displaying greater multimorbidity than patients included in RCTs [32–35], making it challenging to apply these data to everyday practice. Thus, more research is needed to strengthen the capacity of primary care teams to overcome the diabetes epidemic.

2.1. Purpose of position statement

A tremendous volume of high-quality, evidence-informed treatment guidelines for the management of T2D exist and have been widely distributed. While these guidelines have had a profound influence in promulgating clinical practice decisions, they may be too detailed and exhaustive for primary care clinicians. Recent consensus guidelines with complex treatment algorithms for people with T2D and established or risk of CVD have shown greater focus towards a target audience of secondary care specialists, rather than frontline clinicians [11,12,36,37]. In addition, most guidelines lack specific recommendations for patient referral to secondary care [38]. Significant strides have been made in some countries to include the primary care perspective in guideline development, and this position statement aims to complement these efforts and to provide useful guidance for regions where primary care guideline input is lacking.

This position statement aims to provide a simple and pragmatic tool for primary care clinicians and other HCPs worldwide for the pharmacological management of people with T2D and other comorbidities in their role as first point of contact in healthcare. This patient-centred clinical decision-making approach is unique from existing national and international guidelines. It offers a novel risk stratification approach and practical recommendations that can be widely implemented through various primary care systems to help link patients with the appropriate care and prevent diabetes-associated complications. It is not intended to supplant well established national and international guidelines, but rather to provide additional direction and focus to reflect primary care in high-risk patients with T2D. In addition, this consensus paper draws increasing attention to heart failure and cardiorenal syndrome as serious comorbidities associated with T2D.

Box 1 summarises suggestions on how primary care physicians can use this position statement to drive shared decision-making conversations with their patients. Box 2 introduces new, evidence-based criteria for cardiovascular risk stratification of patients with T2D in primary care. Throughout the paper, the key recommendations are collected in callout boxes for easy reference.

Box 1: How to use this position statement

This position statement summarises the current evidence for glycaemic efficacy, cardiovascular and renal risk, and side effects for a wide variety of therapies for T2D.

Box 2 suggests a simple and pragmatic cardiovascular risk assessment to help inform patient-centred treatment decisions.

Boxes 3–8 summarise the treatment recommendations by cardiovascular/renal disease or risk factor

Table 1 summarises the prescribing tips and side effects related to each drug class discussed

3. Methods

This position statement is authored by a group of primary care practitioners convened by Primary Care Diabetes Europe. A comprehensive review of international diabetes guidelines was conducted at a roundtable consensus conference in February 2019. The overall author group consisted of eight primary care clinicians and one nurse with expertise in diabetes representing the European and North American regions. Facilitated by an independent moderator, consensus was reached between all members of the author group on the focus of the position statement and its general framework. All participants were involved in the debate and equally influenced the outcome [39]. Using a Likert scale (of 'strongly disagree', 'disagree', 'agree', and 'strongly agree'), a consensus was achieved when agreement exceeded 90% of the votes.

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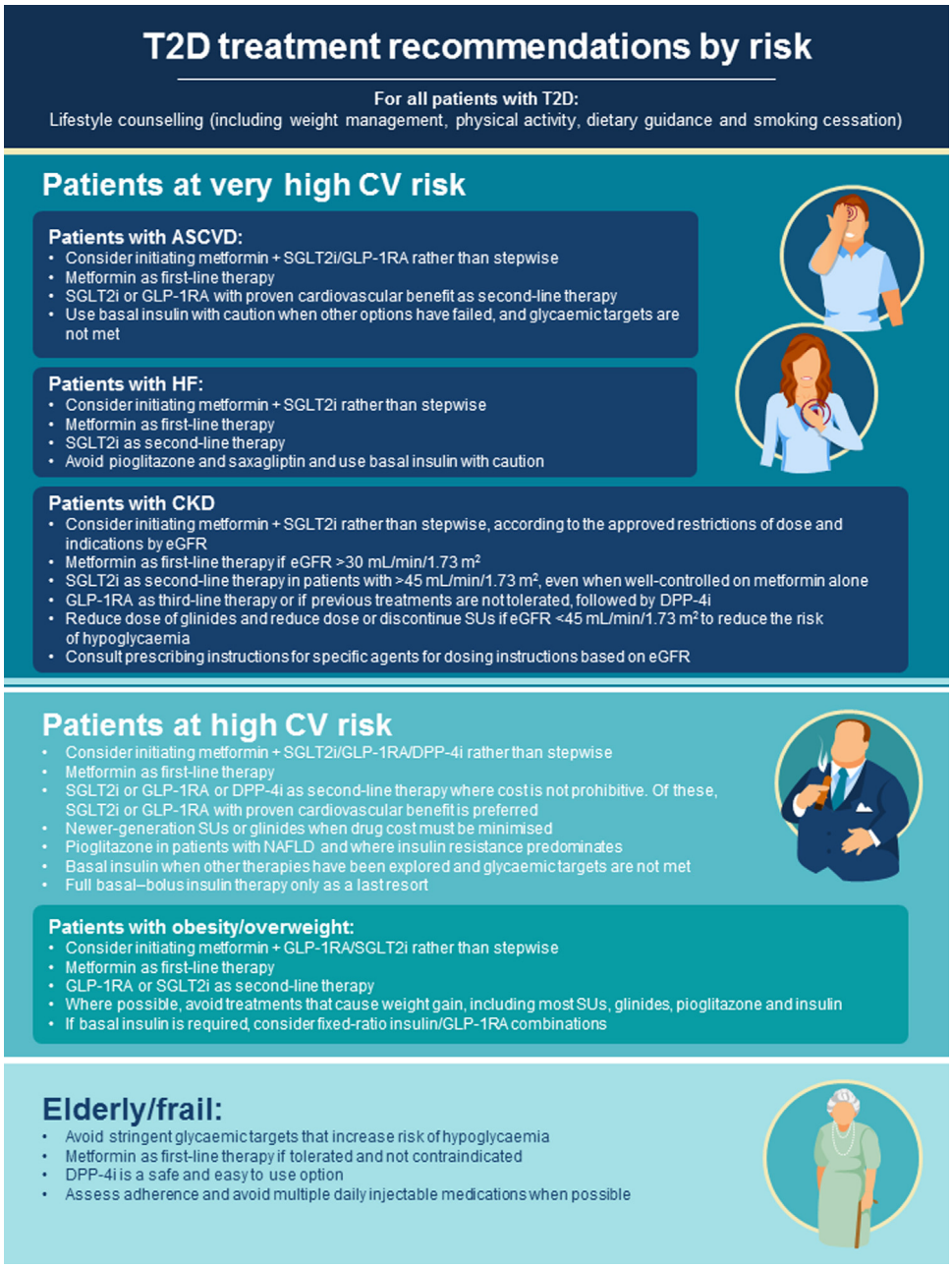

Fig. 1. Visual patient assessment checklist.

To assess the currently available research on people with diabetes in primary care, a PubMed literature search was conducted in advance of the consensus conference on epidemiological studies carried out in primary care populations and with the involvement of primary care clinicians within the last 5 years. Search terms included 'diabetes', 'cardiovascular disease', 'prevalence', 'primary care', and 'Europe' [18]. These results were shared at the consensus conference, followed by a series of presentations organised by drug family [40]. Each individual presentation replicated a common format, from discussing the different compound options available within each family, to a detailed review of current evidence supporting the use of each compound/drug family in the primary and secondary prevention of CVD in patients with T2D. These presentations helped to lay the foundational knowledge for further discussion on the gaps in existing guidelines and the need for specific treatment recommendations for primary care clinicians.

3.1. Synthesis of the position statement

To assess the most recent data on optimal treatment of T2D, a detailed and focused literature review (PubMed, Medline, Web of Science, Google Scholar and Ebsco CINAHL) was undertaken to identify English language articles published since 2015. Search terms included 'type 2 diabetes', 'cardiovascular disease', 'global', 'prevalence', 'primary care', and 'therapeutic inertia'. Given the breadth of this consensus statement, review articles were also included. The latest consensus guidelines from the European Association for the Study of diabetes (EASD) with the American Association of Diabetes (ADA), and from the European Society of Cardiology (ESC) on managing hyperglycaemia in T2D were reviewed, as well as articles cited within [11,12,37]. Additional landmark studies and publications were suggested by the authors. The authors discussed the identified literature and

Table 1
Common side effect and prescribing tips for the use of anti-hyperglycaemic medication in the treatment of type 2 diabetes.

Category of drug	Physiological mode of action	Most common side effects	Prescribing tips
Metformin	Decreases hepatic glucose production [11,12].	GI symptoms [11,12].	GI symptoms can be limited by gradual dose escalation or dose reduction [200].
Glinides	Increase insulin secretion [11,12].	Modest weight gain, low risk of hypoglycaemia [150].	
GLP-1 receptor agonists	Enhance glucose-dependent insulin production, suppress glucose-dependent glucagon secretion, slow gastric emptying, suppress appetite [11,12].	GI symptoms including nausea, diarrhoea, vomiting, decreased appetite, abdominal pain, constipation [169,170], gallstones[171], possible increased risk of acute pancreatitis [172].	Nausea, other GI symptoms and diabetic retinopathy risks can be limited by dose escalation [201]. If patients do not tolerate a gradual dose escalation, consider delaying dose escalation by one additional week. It is also recommended to have more frequent and smaller meals to reduce the risk of GI side effects.
		An increased risk of diabetic retinopathy was observed with semaglutide in SUSTAIN 6 trial [71].	Patients are advised to use a different injection site each week to avoid injection site reactions [169,170].
SGLT2 inhibitors	Enhance excretion and prevent reabsorption of urinary glucose [11,12].	Urogenital tract infections (with higher risk in women and potential greater impact on quality of life in the elderly) [95,202,203], dehydration and hypotension from increased urination, risk of lower limb amputations [96,204].	Monitor and treat urogenital infections as needed.
		Some concerns of increased risk of bladder cancer with dapagliflozin treatment [205].	In conditions of reduced oral intake or potential fluid losses such as gastrointestinal illness, carefully monitor volume status and discontinue treatment until fluid loss is corrected [206]. Be cautious of other pre-existing factors that could increase fracture risk, such as history of fractures and higher risk of falls. Encourage proper hygiene in both female and male patients to avoid genital mycotic infections [96,97,206].
DPP-4 inhibitors	Enhance glucose-dependent insulin production, suppress glucose-dependent glucagon secretion [11,12].	Upper respiratory tract infection, urinary tract infection, nasopharyngitis and headache [207–209], risk of HF [103].	
Sulphonylureas	Increase insulin secretion [11,12].	Hypoglycaemia, weight gain [210].	Hypoglycaemia usually occurs due to excessive dosage; use with caution in situations in which hypoglycaemia is most likely to occur. Weight gain is usually countered by the concurrent administration of metformin [210]. Only gliclazide may be used in CKD stage 3 or worse. For all others, dose should be reduced in subjects with eGFR 60–90 mL/min/1.73 m^2. Contraindicated in subjects with eGFR < 60 mL/min/1.73 m^2 [211]. Even in the case of gliclazide, a hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.
Acarbose	Reduces rate of absorption of carbohydrates.	Flatulence, mild diarrhoea.	Side effects may be mitigated if the dose is increased slowly [168].
Pioglitazone	Enhances insulin sensitivity [11,12].	Weight gain, swelling, risk of bone fracture, bone loss [11,12,212]. Should not be used in patients with history of or active bladder cancer [163] or those at risk of HF [160].	
Insulin	Stimulates insulin receptor leading to increased insulin disposal and decreased production of glucose [11,12].	Hypoglycaemia, weight gain [11,12].	If hypoglycaemia develops, consider reducing dose or modifying timing of injection. Patients should be encouraged to rotate injection sites.

DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HF, heart failure; SGLT2, sodium-glucose co-transporter-2.

assessed its relevance using the consensus approach outlined above.

This consensus statement was drafted with the support of a writing group, followed by cycles of review and revision of the manuscript. The focus of the position statement and section headings were further refined through various rounds of correspondence until consensus was reached between all members of the author group. A draft was reviewed at a second author group meeting in September 2019 to discuss and collect additional feedback. Review of the updated draft was then invited by a diabetologist and a primary care physician external to the consensus statement process and their comments considered by the authors.

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4. Visual patient assessment checklist and prescribing tips by drug class

Fig. 1 shows a visual summary of the recommendations of this position statement. More information for the summarised recommendations can be found in Section 5.

Side effects are major factors influencing treatment choice and medication adherence [41]. Patients will have their personal needs, preferences and tolerances regarding the route of administration (injectable or oral), discomfort, side effects, and the price they are willing to pay out of pocket. Shared decision making is an approach in which patients and clinicians work together and engage in a deliberate dialogue about reasonable treatment options. In this process, the HCP is the expert in evidence-based medicine and should suggest the most clinically appropriate and safe medications [42]. This approach is feasible in primary care [15]. Table 1 summarises the most common and serious side effects that should be taken into consideration when choosing the most appropriate treatment regimen, as well as relevant prescribing tips to ensure minimal occurrence or impact of these side effects.

5. Treatment recommendations stratified by risk

5.1. Metformin and lifestyle modifications

As part of their first-line therapy, all patients with T2D should be offered individualised and comprehensive lifestyle counselling including weight management, physical activity, dietary guidance, and smoking cessation. All glycaemic and lifestyle goals should be co-developed and agreed to by the patient and physician. For patients who find it challenging to meet their glycaemic goals, therapeutic lifestyle modifications and adherence to these measures should be discussed at ongoing follow-up visits every 3–6 months [11,12]. In addition to healthy lifestyle management, newly diagnosed patients with T2D should also be treated with metformin as the first-line pharmacological therapy of choice. Clinicians have over 60 years of experience using metformin [43], thus its risks and benefits are well understood. Metformin is a cost-effective option for glucose lowering, associated with weight loss and fewer hypoglycaemic episodes when compared to insulin or sulphonylureas (SUs) [11,12,44]. Some evidence suggests it has cardiovascular benefit with respect to myocardial infarction (MI) [44,45], but the paucity of data from long-term cardiovascular outcome trials (CVOTs) creates uncertainty around the effect of metformin in reducing CVD in patients with T2D [46]. Importantly, metformin has been shown to be associated with gastrointestinal side effects, affecting nearly 25% of patients, among which 5% develop complete intolerance [47]. These side effects can often be successfully mitigated with careful dose titration.

Evidence is emerging to support the initiation of a second therapeutic agent along with metformin, rather than waiting for treatment failure with metformin before intensification [48,49]. These data are supported by evidence of 'glycaemic legacy', whereby reduced risk of complications is seen in some studies where patients are treated intensively early in their disease progression, even if this stringent glycaemic control is eventually relaxed [50,51]. It should be noted, however, that evidence for this glycaemic legacy effect is not supported by all follow up studies [52]. To avoid therapeutic inertia, dual therapy may be considered at diabetes diagnosis in patients who are likely to benefit from better glycaemic control. The decision of whether to initiate dual therapy at diagnosis should consider individual patient characteristics and treatment goals. If a dual therapy approach is used, patients with cardiovascular or renal disease could gain the benefits of agents shown to reduce risk of cardiovascular events or improve renal parameters (outlined below) earlier in their treatment progression. If metformin monotherapy is chosen at diagnosis, patients should be monitored closely and treatment intensified every 2–4 weeks if glycaemic targets are not met to avoid therapeutic inertia [53]. For patients on dual therapy and not meeting treatment goals, additional intensification should be strongly considered to avoid therapeutic inertia.

5.2. Assessing risk in patients with T2D

CVD represents one of the most prevalent comorbidities of T2D [5], affecting nearly one-third of all patients globally [10]. The World Health Organization defines CVD as a group of conditions related to the heart and blood vessels, including coronary heart disease, cerebrovascular disease, and peripheral arterial disease [54].

Understanding the intricate pathophysiological link between CVD and T2D is useful for clinicians when choosing the most suitable and effective treatment for their patients. The physiological mechanisms driving diabetic cardiomyopathy can be used to explain the profound impact of T2D on the cardiovascular system. Most people with T2D have hyperglycaemia, hyperlipidaemia, hypertension, and overweight, all of which confer substantial CVD risk. Diabetes guidelines and intervention strategies therefore mandate an intensified treatment approach to reduce the risk for diabetes-related complications [11,12,55].

Awareness and knowledge of all cardiovascular risk factors are critical in determining CVD risk. When primary prevention strategies fail due to pervasive or unmodifiable risk factors, secondary prevention efforts become important, with focus on early detection to preserve quality of life of the patient [56].

We propose here a pragmatic, evidence-based cardiovascular risk stratification tool intended to complement the tool provided by American College of Cardiology/American Heart Association and endorsed by American Diabetes Association [57,58], and guide primary care physicians in their choice for the treatment of patients with T2D (Box 2).

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Box 2: Cardiovascular risk stratification in patients with T2D

Patients with T2D are considered to be at *very high cardiovascular risk* if they have any of the following:

1. History of CVD (A)
2. Multiple uncontrolled CVD risk factors, including hypertension, hyperlipidaemia, obesity, smoking and/or physical inactivity (A)
3. eGFR <60 mL/min/1.73 m^2 (B)
4. Albuminuria (B)
5. Age at diagnosis <40 years (C)

All other patients with T2D are considered to be at *high cardiovascular risk*

Letters (A–C) denote level of evidence based on the American Diabetes Association grading system: A, clear evidence from well-conducted, generalisable RCTs, that are adequately powered, including 1) evidence from a well-conducted multicentre trial or meta-analysis that incorporated quality ratings in the analysis, 2) compelling nonexperimental evidence, 3) supportive evidence from well-conducted RCTs that are adequately powered; B, supportive evidence from a well-conducted cohort study or case-control study; C, supportive evidence from poorly controlled or uncontrolled studies, or conflicting evidence with the weight of evidence supporting the recommendation; E, expert opinion.

5.2.1. Rationale for risk stratification criteria

History of established CVD is one of the most widely recognised and important predictors of future major adverse cardiovascular events (MACE) [59]. Similarly, both decreased estimated glomerular filtration rate (eGFR) and albuminuria are strong independent predictors of MACE in patients with T2D [60]. Finally, there is evidence to suggest that early-onset T2D represents an aggressive form of the disease in terms of cardiovascular risk [61], reflected in the fact that patients with a younger age at diagnosis have a much higher cardiovascular risk than that of age-matched controls [62]. Thus, patients with any of these characteristics are considered to be at very high cardiovascular risk.

Since T2D itself is considered a major risk factor for CVD, the remaining patients who do not fit these criteria are considered to be at high cardiovascular risk.

5.3. Patients at very high cardiovascular risk

The relationship between glucose lowering and CVD in diabetes is unclear [63]. The ACCORD trial demonstrated that intensive glucose lowering therapy alone did not translate into a statistically significant or clinically relevant reduction in adverse cardiovascular outcomes. Results from this study suggested a lesser benefit in the first occurrence of nonfatal MI, nonfatal stroke, or death from cardiovascular causes in patients that had previously experienced a cardiovascular event [64]. A subsequent large meta-analysis corroborated these results, showing intensive glucose lowering treatment had essentially no benefit in reducing risk of cardiovascular events [65]. Episodes of severe hypoglycaemia, which can sometimes occur as a consequence of stringent glycaemic targets, are a strong predictor of adverse cardiovascular events and mortality [66]. However, other meta-analyses and long-term follow ups do suggest a modest risk reduction for certain macrovascular events for patients treated using long-term intensive glucose-lowering strategies [50,67,68].

Given these conflicting results, patients at very high cardiovascular risk, and particularly those prone to hypoglycaemia, may benefit from a treatment regimen that balances moderate glycaemic targets with use of agents with proven benefits to cardiovascular risk and renal parameters, as outlined below. A summary of outcome trials and their results examining the cardiovascular and renal effects of various anti-glycaemic treatments is shown in Table 2.

5.4. Patients with atherosclerotic cardiovascular disease (ASCVD)

ASCVD is the primary cause of morbidity and mortality in individuals with T2D [58]. ASCVD is broadly defined as atherosclerosis leading to coronary artery disease, cerebrovascular disease, or peripheral arterial disease [58]. While differences exist in how ASCVD is reported across clinical trials, all CVOTs have enrolled some proportion of patients with established CVD (prior MI, stroke, or arterial revascularisation), and a range of patients with clinically significant atherosclerosis (prior transient ischaemic attack, hospitalised unstable angina, amputation, congestive heart failure (HF) New York Heart Association class II–III, >50% stenosis of any artery, symptomatic or asymptomatic coronary artery disease documented by imaging, CKD with eGFR < 60 mL/min/1.73 m^2) [11,12].

When deciding on the most appropriate and effective antihyperglyaemic medication to add after or with metformin, it is important to consider the presence of other diabetes-associated comorbidities. The presence of ASCVD in people with T2D strongly advocates choosing a glucose-lowering drug that controls and prevents the worsening of ASCVD, hospitalisation for HF, renal disease and mortality. Therapy in patients at increased risk of stroke should also be focused on lowering blood pressure, which has been shown to dramatically lower risk [69].

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Table 2
Summary of outcome trials.

Category of drug	Outcome trial	Comparator	Population	Prior CVD	Median follow up	Primary composite endpoint	Primary endpoint HR (95% CI), p-value	All-cause mortality HR (95% CI), p-value	Number needed to treat to prevent 1 event
GLP-1RAs									
Lixisenatide	ELIXA **E**valuation of **LIX**isenatide in **A**cute coronary syndrome	Placebo	6068	100%	25 months	4-point MACE	1.02 (0.89; 1.17), $p < 0.001$ for non-inferiority; $p = 0.81$ for superiority [76]	0.94 (0.78; 1.13), $p = 0.50$	–
Exenatide	EXSCEL **EX**enatide **S**tudy of **C**ardiovascular **E**vent **L**owering	Placebo	14,752	73%	3.2 years	3-point MACE	0.91 (0.83; 1.00), $p < 0.001$ for non-inferiority; $p = 0.06$ for superiority [77]	0.86 (0.77; 0.97), $p = 0.016$	–
Liraglutide	LEADER **L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of Cardiovascular Outcomes **R**esults	Placebo	9340	81%	3.8 years	3-point MACE	0.87 (0.78; 0.97), $p < 0.001$ for non-inferiority; $p = 0.01$ for superiority [70]	0.85 (0.74; 0.97), $p = 0.02$	Primary outcome (over 3 years): 66 Death from any cause (over 3 years): 98
Semaglutide	SUSTAIN-6 Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes	Placebo	3297	83%	2.1 years	3-point MACE	0.74 (0.58; 0.95), $p < 0.001$ for non-inferiority; $p = 0.02$ for superiority [71]	1.05 (0.74; 1.50), $p = 0.79$	Primary outcome (over 24 months): 45 Risk of major CV event (over 3 years): 31 [213]
Oral semaglutide	PIONEER 6 Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes	Placebo	3183	84.6%	15.9 months	3-point MACE	0.79 (0.57; 1.11), $p < 0.001$ for non-inferiority; $p = 0.17$ for superiority [72]	0.51 (0.31; 0.84), no p value reported	–
Albiglutide	HARMONY Outcomes Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease	Placebo	9463	100%	1.5 years	3-point MACE	0.78 (0.68; 0.90), $p < 0.0001$ for non-inferiority; $p = 0.0006$ for superiority [74]	0.95 (0.79; 1.16), $p = 0.644$	Primary event outcome (over 1.6 years): 50
Dulaglutide	REWIND **R**esearching Cardiovascular **E**vents with a **W**eekly **I**ncretin in **D**iabetes	Placebo	9901	31%	5.4 years	3-point MACE	0.88 (0.79; 0.99), $p = 0.026$ for superiority [75]	0.90 (0.80; 1.01), $p = 0.067$	For people with a previous CV event (over 5 years): 18
SGLT-2i									
Empagliflozin	EMPA-REG OUTCOME Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes	Placebo	7020	99%	3.1 years	3-point MACE	0.86 (0.74; 0.99), $p < 0.001$ for non-inferiority; $p = 0.04$ for superiority [79]	0.68 (0.57; 0.82), $p < 0.001$	Risk of MACE (over 3.1 years): 63 [214] Risk of death from any cause (over 3 years): 39
Canagliflozin	CANVAS Canagliflozin Cardiovascular Assessment Study	Placebo	10,142	66%	126.1 weeks	3-point MACE	0.86 (0.75; 0.97), $p < 0.001$ for non-inferiority; $p = 0.02$ for superiority [80]	0.87 (0.74; 1.01), p = 0.24 for superiority	Additional major CV event (over 3 years): 179 [213]

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Table 2 (*Continued*)

Category of drug	Outcome trial	Comparator	Population	Prior CVD	Median follow up	Primary composite endpoint	Primary endpoint HR (95% CI), p-value	All-cause mortality HR (95% CI), p-value	Number needed to treat to prevent 1 event
Canagliflozin	CREDENCE **C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation	Placebo	4401	50.4%	2.62 years	ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59; 0.82); $p = 0.00001$ [123]	0.83 (0.68; 1.02), no *p*-value reported	Primary outcome: 22 (15; 38) Composite outcome of ESKD, doubling of serum creatinine, or renal death (over 2.62 years): 28 ESKD events (over 2.62 years): 43 HHF: 45 Composite events of CV death, MI, or stroke (over 2.62 years): 40
Dapagliflozin	DECLARE-TIMI 58 Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58	Placebo	17,160	41%	4.2 years	3-point MACE	0.93 (0.84; 1.03), $p = 0.17$ for superiority [81]	0.93 (0.82; 1.04), No *p*-value reported	CV death or HHF in patients with prior MI (over a period of 4 years): 53 [214]
Dapagliflozin	DAPA-HF **D**apagliflozin **A**nd **P**revention of **A**dverse-outcomes in **H**eart **F**ailure)	Placebo	4744	100%	18.2 months	Worsening heart failure or death from CV causes	0.74 (0.65–0.85), $p < 0.001$ for superiority [92]	0.83 (0.71; 0.97), No *p*-value reported	Primary outcome: 21
DPP-4i									
Alogliptin	EXAMINE Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care	Placebo	5380	100%	18 months	3-point MACE	0.96 ($\leq$1.16), $p < 0.001$ for non-inferiority; p = 0.32 for superiority [215]	0.88 (0.71; 1.09), $p = 0.23$	
Saxagliptin	SAVOR-TIMI 53 Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction	Placebo	16,492	90.9%	2.1 years	3-point MACE	1.00 (0.89; 1.12), $p = 0.99$ for superiority; $p < 0.001$ for non-inferiority [216]	1.11 (0.96; 1.27), $p = 0.15$	–
Linagliptin	CARMELINA **CA**rdiovascular safety and **R**enal **M**icrovascular Outcom**E** with **Lina**gliptin in Patients With Type 2 Diabetes	Placebo	7003	57%	2.2 years	3-point MACE	1.02 (0.89; 1.17), $p < 0.001$ for non-inferiority; $p = 0.74$ for superiority [106]	0.98 (0.84; 1.13), $p = 0.74$	–
Linagliptin	CAROLINA **CAR**diovascular **O**utcome Study of **LINA**gliptin Versus Glimepiride in Patients with Type 2 Diabetes	Glimepiride	6033	35%	6.3 years	3-point MACE	0.98 (0.84; 1.14), $p < 0.0001$ for non-inferiority; $p = 0.76$ for superiority [217]	0.91 (0.78; 1.06), *p*-value not significant	–
Insulin									
Insulin degludec	DEVOTE Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events	Insulin glargine U100	7637	85.2%	1.83 years	3-point MACE	0.91 (0.78; 1.06), $p < 0.001$ for noninferiority [83]	0.91 (0.76; 1.11), $p = 0.35$	–

CV, cardiovascular; ESKD, end-stage kidney disease; HHF, hospitalisation for heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction.

5.4.1. Glucagon-like peptide-1 receptor agonists

There is substantial evidence from large CVOTs corroborating the use of some glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with T2D and established ASCVD. GLP-1RAs are recommended for initial intensification. Among the list of trials that investigated this drug class, the LEADER trial demonstrated superiority of liraglutide compared to placebo in reducing the risk of death from cardiovascular causes, nonfatal (including silent) MI or nonfatal stroke [HR: 0.87 (0.78; 0.97), number needed to treat (NNT): 66–67 over 3 years] [70]. In the SUSTAIN 6 trial that compared the injectable GLP-1RA semaglutide to placebo, the rate of cardiovascular death, nonfatal MI or nonfatal stroke was 26% lower among patients receiving semaglutide than among those receiving placebo [HR: 0.74 (0.58; 0.95), NNT: 45 over 24 months]. Based on the design of the study, this result reflects noninferiority of semaglutide compared to placebo. Semaglutide had a neutral effect on the number and rate of occurrence of severe hypoglycaemic episodes [71]. The oral formulation of semaglutide also demonstrated noninferiority to placebo in the PIONEER 6 trial, achieving its primary objective of no excess cardiovascular risk [HR: 0.79 (0.57; 1.11)] [72]. Although the overall number of retinopathy events was low, there was an unexpected higher rate of retinopathy complications (vitreous haemorrhage, blindness, or the need for treatment with an intravitreal agent or photocoagulation) in the semaglutide group in both studies [71,72]. Most cases were non-proliferative, were identified during routine examination, and resulted in no new treatment. In addition, the increase was observed only in patients with previous retinopathy and in patients with the greatest and most rapid reduction in HbA_{1c}, similar to effects seen with insulin and in patients with type 1 diabetes [73].

To further add to the repertoire of CVOTs in patients with T2D and established CVD, the Harmony Outcomes trial confirmed albiglutide was superior to placebo in reducing MACE [HR: 0.78 (0.68; 0.90), NNT: 50 over 1.6 years] [74]. More recently, results from the REWIND trial showed the addition of dulaglutide to existing diabetes treatment reduced the primary composite of cardiovascular outcomes over 5 years in a broad range of people with T2D [HR: 0.88 (0.79; 0.99), NNT for patients with a prior cardiovascular event: 18 over 5 years]. REWIND differed from preceding CVOTs with GLP-1RAs in that only 31% of participants had established CVD [75]. Of note, in the REWIND trial the risk of eye outcomes was numerically higher with dulaglutide compared with the placebo group [75].

Despite the well-recognised benefit of GLP-1RAs in effectively altering the rate of MACE, it is also important to address that some drugs of this class have not been shown to significantly improve cardiovascular outcomes. Neither lixisenatide [HR: 1.02 (0.89; 1.17)] nor exenatide [HR: 0.91 (0.83; 1.00)] showed significant improvements in risk of MACE [76,77]. Overall, a recent systematic review of GLP-1RA CVOTs identified a class effect for risk reduction of MACE, cardiovascular mortality and all-cause death [78]. Patients and HCPs should also discuss the considerable inter-individual variation in magnitude of effect on HbA_{1c} and weight loss in patients treated with GLP-1RAs, and continued treatment with these therapies should be evaluated after 6 months.

5.4.2. Sodium–glucose co-transporter-2 inhibitors

Among the sodium–glucose co-transporter-2 inhibitors (SGLT-2is), empagliflozin and canagliflozin have demonstrated beneficial effects in reducing MACE in patients with T2D and ASCVD. Almost all patients included in the EMPA-REG OUTCOME trial had previous CVD, and treatment with empagliflozin was shown to reduce risk of the primary MACE endpoint by 14% compared to placebo [HR: 0.86 (0.74; 0.99), NNT: 63 over 3.1 years]. While this trial showed no significant differences in the rates of MI or stroke when treated with empagliflozin, this treatment did lead to significant reductions in rates of death from cardiovascular causes, hospitalisation for HF, and death from any cause [79]. Results from the CANVAS Programme, which included a broad patient population of whom more than 65% had a history of CVD, confirmed the superiority of canagliflozin compared with placebo in significantly lowering the rate of the primary outcome, which was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke [HR: 0.87 (0.75; 0.97), NNT for patients with a prior cardiovascular event: 179 over 3 years] [80]. More recently, the DECLARE-TIMI 58 study (with ~40% of patients with established CVD) did not demonstrate significantly decreased risk of MACE for dapagliflozin compared to placebo [HR: 0.93 (0.82; 1.04)], but did result in decreased rates of cardiovascular death or hospitalisation for HF [HR 0.83 (0.73; 0.95), NNT: 53 over 4 years] [81]. These results were corroborated by a subsequent meta-analysis that confirmed moderate benefits of SGLT2is on atherosclerotic events in patients with established CVD [82].

5.4.3. Insulin

Importantly, insulin should only be used in patients with T2D and ASCVD when other options have been attempted and co-developed glycaemic goals have not been met. Apart from the DEVOTE trial, which demonstrated non-inferiority of insulin degludec to insulin glargine U100 on cardiovascular outcomes [83], there have been no other trials to date that have investigated the cardiovascular safety of insulin in patients with T2D and established CVD. Thus, GLP-1RAs are recommended before insulin as the first injectable treatment by a number of clinical practice guidelines [11,12,37].

Ultimately, SGLT-2is (empagliflozin, canagliflozin and dapagliflozin, with a probable class effect) and GLP-1RAs (liraglutide, semaglutide, albiglutide, and dulaglutide) have been the only drug families to show proven CV benefit in patients with T2D and ASCVD.

Box 3: Treatment recommendations for patients with ASCVD

- Consider initiating metformin + SGLT2i/GLP-1RA rather than stepwise (E)
- Metformin as first-line therapy (A)
- SGLT2i or GLP-1RA with proven cardiovascular benefit as second-line therapy (A)
- Use basal insulin with caution when other options have failed, and glycaemic targets are not met (E)

5.5. Patients with HF

HF is an increasingly common comorbidity associated with T2D, with up to 40% prevalence in patients with T2D and a median patient survival rate of only around 4 years [84–86]. Increased risk

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of HF in patients with T2D has been shown to be associated with greater insulin use and poor glycaemic control [87]. Despite the poor prognosis and high medical demand for effective therapies for patients with diabetes and HF, treatment options remain scarce [85,88,89].

5.5.1. Sodium–glucose co-transporter-2 inhibitors

There is good evidence supporting the use of SLGT-2is in patients with T2D and heart failure with reduced ejection fraction (HFrEF), with demonstrated favourable effects on cardiovascular outcomes, in addition to reducing hyperglycaemia [90]. The first drugs of this class available for the treatment of T2D that were shown to improve the risk of hospitalisation for HF were empagliflozin and canagliflozin [79,80,91]. Post hoc analyses of data from the EMPA-REG OUTCOME showed that empagliflozin resulted in significant reductions in hospitalisation for HF, as well as in death from cardiovascular causes, for patients with and without HF at baseline [90]. Results from the CANVAS Programme suggest that the significant reduction in the risk of hospitalisation for HF with canagliflozin may be greater in patients with prior history of HF compared to those without [91]. Furthermore, dapagliflozin was more recently shown to lower the rates of cardiovascular death and hospitalisation for HF in a broad patient population. Although similar reductions were seen in patients regardless of history of ASCVD or HF, only 10% of patients had a history of HF [81]. The DAPA-HF study sought to further examine the patient population with established HF and showed benefits in reduced hospitalisation for HF and mortality in patients with HF with and without diabetes [92]. This trial is the first to show benefits specifically in patients with prior HF without diabetes and reinforces the use of these drugs in this population. The primary endpoint of the study, the composite of a first episode of worsening HF or cardiovascular death, occurred in 16.3% in the dapagliflozin group and in 21.2% in the placebo group [HR: 0.74; (0.65; 0.85), NNT: 21].

While these clinical trial data examine patients with HFrEF, heart failure with preserved ejection fraction (HFpEF) has been less well studied, despite its common association with T2D. However, the CVD-REAL real-world evidence study showed reduced risk of hospitalisation for any HF and mortality in patients taking SGLT2is [93]. Clinical trials examining SGLT2i treatment specifically in patients with HFpEF are currently ongoing.

Despite their benefits, patients and physicians should be aware that an increased risk of lower limb amputation was observed in patients treated with canagliflozin in the CANVAS Programme, but not in other trials with SGLT2is [94]. That said, patients should be cautious of other pre-existing factors that increase fracture risk. Physicians should also encourage proper hygiene in both female and male patients to avoid genital mycotic infections common with this class of drug (and which may affect treatment adherence) [95–98]. Patients should also be counselled to maintain adequate fluid intake to prevent dehydration and hypotension from increased urination. Physicians should also be aware of the risk of diabetic ketoacidosis and the rarer but highly severe Fournier gangrene.

5.5.2. Thiazolidinediones

Certain drug families should also be particularly avoided when treating patients with T2D and HF. The PROactive trial demonstrated that the thiazolidinedione pioglitazone was associated with a 50% increase in hospitalisation for HF compared to patients treated with placebo [99]. A meta-analysis of randomised-controlled trials studying the effect of pioglitazone in secondary prevention of established CVD showed increased risk of HF despite lowered risk of recurrent MACE, stroke and MI [100]. Direct comparison trials assessing the incidence of cardiovascular events between pioglitazone and other antihyperglycaemic medications is limited to the TOSCA.IT trial, which compared pioglitazone with SUs (mostly glimepiride and gliclazide) which showed a non-statistically significant but numerically higher risk of HF in patients treated with pioglitazone [101]. Thus, pioglitazone is not recommended in the treatment of patients with T2D and HF, due to its demonstrated increased risk in HF-associated adverse cardiovascular effects, as well as the inadequacy of robust data from multiple dedicated trials.

5.5.3. Dipeptidyl peptidase-4 inhibitors

To date, there is no demonstrated benefits on CV outcomes of DPP-4 inhibitors (DPP-4is), and caution may be warranted in T2D patients with HF [102]. In the SAVOR-TIMI 53 trial, saxagliptin was associated with an increased relative risk of hospitalisation for HF, which was higher among patients with prior HF [103]. Furthermore, in a post hoc analysis, a small increase in hospitalisation for HF was observed in patients without a history of HF randomised to receive alogliptin in the EXAMINE trial, compared to those assigned to placebo; however, an interaction between treatment and history of HF was not found in the analysis, and there was no statistically-significant difference between the two treatment groups in all-cause death and hospitalisation for HF, irrespective of history of HF [104]. The two other CVOTs examining DPP-4is, TECOS examining sitagliptin and CARMELINA evaluating linagliptin, failed to demonstrate any significant difference in the rate of hospitalisation for HF between the DPP4i and placebo groups [105,106].

5.5.4. Insulin

Insulin treatment has been associated with renal sodium retention and oedema, particularly when used in combination with thiazolidinediones [107,108]. Assessing whether insulin treatment worsens HF has been difficult, given that patients treated with insulin typically have more advanced T2D and a greater degree of comorbidity and thus, clinical severity. However, a recent meta-analysis showed that insulin treatment in patients with HF was associated with a higher risk of death and hospitalisation for HF, irrespective of diabetes duration [109]. For those with HF, patients and HCPs should carefully weigh the benefits of stricter glycaemic control against the risks of worsening HF, with reduced insulin intensification given serious consideration.

In conclusion, SGLT-2is may be beneficial and are recommended for the treatment of patients with T2D and HF. Saxagliptin, pioglitazone and insulin treatment should be used with caution in patients who develop or have a history of HF. GLP-1RAs and DPP4is other than saxagliptin have not shown any benefits or harms in the risk for HF in patients with T2D.

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Box 4: Treatment recommendations for patients with HF

- Consider initiating metformin + SGLT2i rather than stepwise (E)
- Metformin as first-line therapy (A)
- SGLT2i as second-line therapy (A)
- Avoid pioglitazone (A) and saxagliptin (A) and use basal insulin with caution (B)

5.6. Patients with chronic kidney disease

Diabetes is the leading cause of CKD, and ~40% of people with T2D also have CKD [110]. The kidney microvasculature is particularly sensitive to the damaging effects of hyperglycaemia, leading to impaired renal function [111]. Importantly, CKD puts limitations on the glucose-lowering therapies that can be used [112], making good glycaemic control increasingly difficult. Although these patients are at very high cardiovascular risk, patients and physicians are encouraged to choose as stringent glycaemic targets as are deemed safe to limit the worsening of microvascular disease [113].

Patients with established CKD should use metformin cautiously, and it should be discontinued entirely if eGFR falls below 30 mL/min/1.73 m^2 [114]. The use of SU in individuals with CKD is dependent on the level of renal impairment and risk of hypoglycaemia. Reduced doses of glibenclamide and glimepiride are warranted in patients with reduced renal function [112]. In the ADVANCE study, intensive glucose lowering with gliclazide MR significantly reduced the risk of new-onset microalbuminuria by 9%, macroalbuminuria by 30%, new or worsening nephropathy by 21% and end-stage renal disease (ESRD) by 65% [115]. A persistent benefit of this intensive glucose control with respect to ESRD was observed for 10 years after initiation of therapy [116]. Gliclazide and gliclazide MR, with their lower risk of hypoglycaemia, does not require dose reduction in patients with eGFR above 30 mL/min/1.73 m^2 [117]. Compared to other SUs, gliclazide treatment has been associated with lower risk of CVD and with weight neutrality [118].

The insulin secretagogue glinides can also be used in patients with CKD as they are largely metabolised by the liver, though reduced dosages are suggested to limit the risk of hypoglycaemia [119].

DPP-4is are an important option in patients with CKD who are not meeting their glycaemic targets. The different available DPP-4is are metabolised and eliminated in different ways, and decreased doses in patients with varying levels of decreased kidney function may be required according to the prescribing instructions [112]. Of note, linagliptin is excreted almost entirely through a hepatic route and can be used at all stages of CKD without dose adjustment [112].

The GLP-1RA CVOTs have shown this drug family to have positive effects on renal function, particularly reducing albuminuria [120]. GLP-1RAs are therefore of benefit to patients with even severely impaired renal function, particularly those at high risk for CVD, although there is currently no evidence in patients with ESRD, and therefore GLP-1RAs are not recommended in these patients. No dose reduction is required for the long-acting GLP-1RAs liraglutide, dulaglutide and semaglutide in patients with eGFR > 15 mL/min/1.73 m^2 as they are not excreted renally.

For prevention and treatment of diabetic nephropathy with eGFR > 45 mL/min/1.73 m^2, the SGLT2is are perhaps the most useful. At first, there was concern regarding the use of SGLT2is in patients with reduced renal function due to their mechanism of action of inhibiting renal glucose transport [121]. However, EMPA-REG OUTCOME (testing empagliflozin), CREDENCE (testing canagliflozin), and DECLARE-TIMI 58 (testing dapagliflozin), along with several meta-analyses, have demonstrated that SGLT2is reduce the risk of overall nephropathy events, creatinine doubling and initiation of renal replacement therapy [82,122–124]. The evidence for renal benefit is sufficient to warrant considering SGLT2i treatment in patients with eGFR 45–60 ml/min/1.73 m^2, even when these patients already exhibit good glycaemic control.

Box 5: Treatment recommendations for patients with CKD

- Consider initiating metformin + SGLT2i rather than stepwise (E), according to the approved restrictions of dose and indications by eGFR
- Metformin as first-line therapy if eGFR >30 mL/min/1.73 m^2 (A)
- SGLT2i as second-line therapy in patients with >45 mL/min/1.73 m^2 (A), even when well-controlled on metformin alone (E)
- GLP-1RA as third-line therapy or if previous treatments are not tolerated (A), followed by DPP-4i (A)
- Reduce dose of glinides and reduce dose or discontinue SUs if eGFR <45 mL/min/1.73 m^2 to reduce the risk of hypoglycaemia (A)
- Consult prescribing instructions for specific agents for dosing instructions based on eGFR (E)

As outlined here, treatment options vary significantly by CKD stage, with significant variations of suggested dose reduc-

tion/discontinuation even within drug classes, so physicians are encouraged to consult prescribing instructions for specific agents.

5.7. Patients at high cardiovascular risk

Since T2D itself is considered a major risk factor for CVD, the remaining patients with T2D but without established CVD, with eGFR > 60 mL/min/1.73 m^2, with normoalbuminuria and aged >40 years at diagnosis are considered to have high cardiovascular risk. In addition, patients with T2D are also likely to have additional cardiovascular risk factors, including overweight/obesity [125]. These patients with diabetes and without CVD but at high cardiovascular risk represent about half of those with T2D treated in primary care.

Lifestyle and nutrition changes in recent decades have led to a global increase in obesity and a cluster of related and interdependent conditions including dyslipidaemia, hypertension, non-alcoholic fatty liver disease (NAFLD), and insulin resistance leading to T2D. Together, this cluster of conditions is sometimes referred to as the metabolic syndrome [126,127]. Increased insulin resistance has been implicated as a precursor to many of these metabolic complications [128]. However, there is a growing appreciation for the heterogeneity of T2D, with only a subset of patients showing very high insulin resistance [129].

As in all patients, understanding the personal health goals and priorities of patients with T2D and without established CVD is critical. That said, there is evidence that patients with T2D are at much higher risk for ASCVD than those without diabetes [130], and CVD remains the most common cause of death in patients with T2D [131], making primary CVD prevention of great importance. In patients with T2D and established CVD, stringent HbA_{1c} targets may not be appropriate given the association between severe hypoglycaemia and increased risk of adverse macrovascular events [132], but primary prevention patients, with their longer life expectancy, may experience microvascular benefits on a regimen of tighter glycaemic control [133]. As noted previously, some studies show that intensive treatment intervention early in the course of disease is associated with long-lasting benefits in reducing diabetes complications [48,50,51].

5.7.1. Sulphonylureas

Despite being one of the first oral anti-diabetic drug classes available, SUs remain some of the most potent agents for lowering HbA_{1c} [134]. In terms of treatment durability, the ADOPT study showed that treatment with the SU glibenclamide resulted in faster progression to treatment failure than with other glucose-lowering agents [135], but more recent studies demonstrated similar treatment durability for SUs compared to newer drugs [136,137].

Despite contradictory results with first-generation therapies, recent analyses on second- and third-generation SUs show they do not increase cardiovascular mortality or macrovascular events in comparison to other commonly used treatments [138]. These results are corroborated by the recently released results of the CAROLINA trial, which showed no difference in MACE with the SU glimepiride compared to the DPP-4i linagliptin in patients at elevated cardiovascular risk, although the risk of hypoglycaemia was significantly higher with SU than with DPP4i [139]. Notably, UKPDS and follow-up studies of its cohort suggested SUs may also have microvascular benefits [50,140]. Because of their robust effects on glycaemic control and established cardiovascular safety, along with the lower cost of SUs compared to other classes of glucose-lowering drugs [141], these agents have a continued role in management of patients with T2D.

Gliclazide is preferable to others in the class [114] due to its improved treatment durability [142] and reduced risk of hypoglycaemia [143]. Additionally, its neutral effects on mortality and CVD were confirmed the ADVANCE trial [144]. Glimepiride can be considered as the next-best choice, with effective glycaemic control and lower rates of hypoglycaemia compared to glibenclamide [145]. While glibenclamide is the only SU available in many pharmacies in low-income countries [146], it is associated with increased mortality [147] and risk of severe hypoglycaemia [148] compared to other drugs in the class and should not be used unless no other options exist.

Drug access and economic factors will necessarily constrain treatment. If access and cost are no issue, DPP-4is, SGLT2is or GLP-1RAs are all preferable to SUs as second-line treatment of T2D. However, newer SUs remain important low-cost treatment options for many patients [11,12,149].

5.7.2. Glinides

The glinides, nateglinide and repaglinide, are insulin secretagogues with a similar mode of action to SUs, but a shorter duration of action [150]. Although they are not widely used, they remain treatment options in some countries, and have a role to play in managing glycaemia in patients with CKD. Although the cardiovascular effects of these treatments has not been extensively examined, repaglinide appears to have a cardiovascular and all-cause mortality profile similar to that of metformin [151]. Glinide therapy is associated with low risk of hypoglycaemia, with some studies showing a lower risk than SUs [150]. Similarly, most studies show that glinide use is associated with modest weight gain, but perhaps less than that seen with SU therapy [150].

5.7.3. Pioglitazone

The insulin sensitiser pioglitazone is an option for patients without established CVD and who are not reaching their HbA_{1c} targets, particularly for patients with a metabolic syndrome profile where insulin resistance predominates. It provides HbA_{1c} reduction similar to metformin [152] with better treatment durability than SUs [153]. In addition to improvements in insulin resistance and therefore glycaemic control, pioglitazone also has beneficial effects on lipid profile [154].

As mentioned previously, pioglitazone treatment has been shown to reduce ASCVD in patients with established CVD, and data exists to suggest it has a similar effect in primary prevention populations [155]. The mechanism behind this cardioprotection may be attenuation of atherosclerosis, demonstrated in patients treated with pioglitazone compared with those taking glimepiride [156,157].

In addition to cardiovascular benefits, pioglitazone has also been shown to be beneficial in treatment of NAFLD and the more severe non-alcoholic steatohepatitis (NASH) by reducing liver fat content and hepatic fibrosis [158]. The pathophysiology of NAFLD/NASH is intimately related to insulin resistance [159], so the beneficial effect of pioglitazone is unsurprising.

Despite its benefits, pioglitazone use is cautioned in some patients. As mentioned previously, it should not be used in patients with symptomatic HF, since treatment with pioglitazone is associated with fluid retention and oedema in some patients, especially when used in combination with insulin or SUs [160]. It is also associated with weight gain [161] and so must be carefully considered in patients focused on weight loss. Pioglitazone treatment has been linked to increased risk of bone fracture, particular in postmenopausal women [162], so should be avoided in these patients and those with previous fracture. Some studies suggest prolonged pioglitazone use may be associated with an increased risk of bladder cancer [163], so its use in patients with history of or active bladder cancer should be avoided.

5.7.4. α-Glucosidase inhibitors

The α-glucosidase inhibitor acarbose slows the rate of digestion and absorption of complex carbohydrates, decreasing postpran-

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dial hyperglycaemia [164]. Acarbose has a modest HbA_{1c} lowering effect that is more pronounced in patients with diets higher in carbohydrates [165]. Most RCTs of acarbose treatment have included patients with impaired glucose tolerance rather than T2D. The results of the effects on acarbose are mixed, with the STOP-NIDDM study showing significantly decreased risk of cardiovascular events in patients with impaired glucose tolerance treated with acarbose compared to placebo, while the ACE trial showed no significant difference in cardiovascular events between secondary prevention patients treated with acarbose compared to placebo [166,167]. A Cochrane systematic review did not find evidence for an effect of acarbose on mortality or morbidity [168]. Acarbose is generally safe, with side effects largely limited to flatulence and mild diarrhoea [164]. Despite its relatively modest effects on glycaemic control, acarbose remains a popular option in some parts of the world, particularly in cultures with diets rich in carbohydrates.

5.7.5. Glucagon-like peptide-1 receptor agonists

As mentioned previously, data from CVOTs demonstrates that the long-acting GLP-1RAs liraglutide, semaglutide, and dulaglutide are cardioprotective [70,71,75]. Although LEADER and SUSTAIN 6 included both primary and secondary CV prevention patients, more than 80% of patients included in both trials had established CVD [70,71]. Thus, there is limited evidence for a protective role in primary prevention for liraglutide and semaglutide. However, nearly 70% of patients in the REWIND trial did not have established CVD, and dulaglutide treatment was still found to reduce the incidence of MACE [HR: 0.88 (0.79; 0.99), $p = 0.026$], so the evidence for dulaglutide in primary prevention of adverse cardiovascular events is somewhat stronger [75]. GLP-1RAs are safe in this population, and their effective glycaemic control without risk of hypoglycaemia makes them an attractive option for glucose control in patients without CVD.

The main adverse effects associated with the use of GLP-1RA are gastointestinal symptoms including nausea, diarrhoea, vomiting, decreased appetite, abdominal pain, and constipation [169,170]. In a recent post hoc analysis of the LEADER trial, an increase in the risk of gallstones and related complications was observed in the liraglutide-treated patients compared to the placebo control group, with consistent trends across all four categories of events (uncomplicated gallbladder stones, complicated gallbladder stones, cholecystitis and biliary obstruction) [171]. Although prescribing guidelines note a possible increased risk for acute pancreatitis, recent analyses of the effects of GLP-1RA treatment have argued against an association [172]. Importantly, GLP-1RA therapy is associated with a small but consistent reduction in blood pressure and an increase in heart rate [173].

5.7.6. Sodium–glucose co-transporter-2 inhibitors

As with the seminal GLP-1RA trials, the majority of patients in EMPA-REG OUTCOME (>99%) and the CANVAS Programme (>60%) had established CVD at baseline, making it difficult to confirm the cardioprotection seen in these trials extends to primary prevention patients [79,80]. However, the DECLARE-TIMI 58 trial explored dapagliflozin vs. placebo in a majority primary-prevention population and showed that the dapagliflozin was associated with a lower risk of cardiovascular death and hospitalisation for HF [81]. Dapagliflozin is therefore a choice to consider for primary prevention patients.

SGLT2is are associated with a clinically relevant decrease in blood pressure, which may be of benefit to the many patients with T2D who also have hypertension [174].

5.7.7. Insulin

If other treatment options have been explored and a patient is still not reaching glycaemic target, insulin should be used to avoid hyperglycaemia-associated microvascular complications. The risk for hypoglycaemia is higher for patients with T2D on insulin than on other glucose-lowering therapies [175]. For patients who have experienced hypoglycaemia, basal insulin analogues may be preferred. First-generation insulin analogues, including insulin glargine and insulin detemir demonstrate reduced risk of nocturnal hypoglycaemia compared to older generation insulins [176,177]. In turn, second-generation insulin analogues such as insulin degludec and insulin glargine U300 show reduced overall hypoglycaemia compared to their first-generation counterparts [178,179]. The choice of basal insulin should be made in a patient-centred manner in the context of informed discussions between patient and physician, taking into account issues of cost and drug access, as well as risk of hypoglycaemia and its impact on quality of life.

Full basal–bolus therapy should only be considered as a last resort when no other options are available, and it is expected to be needed in very few patients. For patients who remain above target after initiation of basal insulin, insulin/GLP-1RA combination therapies may be an attractive alternative to full basal–bolus therapy, leading to reduced weight gain compared to insulin therapy at equivalent or better glycaemic control [180,181].

Because the safety of most glucose-lowering therapies has not been confirmed in pregnancy, metformin and insulin treatment should be considered in women with T2D of childbearing potential [182].

Box 6: Treatment recommendations for patients at high cardiovascular risk

- Consider initiating metformin + SGLT2i/GLP-1RA/DPP-4i rather than stepwise (E)
- Metformin as first-line therapy (A)
- SGLT2i or GLP-1RA or DPP-4i as second-line therapy where cost is not prohibitive (A). Of these, SGLT2i or GLP-1RA with proven cardiovascular benefit is preferred (E)
- Newer-generation SUs or glinides when drug cost must be minimised (A)
- Pioglitazone in patients with NAFLD and where insulin resistance predominates (A)
- Basal insulin when other therapies have been explored and glycaemic targets are not met (E)
- Full basal–bolus insulin therapy only as a last resort (E)

5.8. Patients with obesity

The vast majority of patients with T2D have obesity or are overweight, and approximately 45% of patients with T2D have obesity [125]. Abdominal obesity in particular is the main driver of increasing insulin resistance which causes metabolic syndrome

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[183]. While some weight loss studies fail to confirm CV benefits [184,185], weight loss between 5% and 10% of starting body weight has been shown to be beneficial and should be a healthy lifestyle goal for most patients with T2D [186].

The ADA Standard of Care treatment guidelines include substantial evidence-based advice on weight control through diet and lifestyle and should be consulted when treating patients with obesity [11,12]. Evidence-based patient education programmes are recommended to assist patients and their families to pursue goals of weight management and healthy lifestyle.

It is important to keep in mind that many glucose-lowering agents cause weight gain, including most SUs, glinides, pioglitazone and insulin [187].

Where possible, glucose-lowering therapies that promote weight loss should be used in patients who would benefit from weight management. Modest weight reductions are seen in patients treated with SGLT2is [79–81]. Small but significant weight reductions are seen in patients treated with the GLP-1RAs lixisenatide (0.7 kg difference compared to the placebo group) and dulaglutide (1.5 kg compared to placebo) [75,76]. More substantial weight loss is seen in patients treated with the GLP-1RAs liraglutide (-2.3 kg vs. placebo) and s.c. and oral semaglutide (-4.3 and -3.4 kg vs. placebo, respectively) [70,71]. Overall, GLP-1RAs and SGLT2is are recommended for patients focusing on weight loss. For patients who require insulin treatment, fixed-ratio insulin/GLP-1RA combinations have been shown to mitigate insulin-associated weight gain [180,181].

Box 7: Treatment recommendations for patients with obesity

- Consider initiating metformin + GLP-1RA/SGLT2i rather than stepwise (E)
- Metformin as first-line therapy (A)
- GLP-1RA or SGLT2i as second-line therapy (A)
- Where possible, avoid treatments that cause weight gain, including most SUs, glinides, pioglitazone and insulin (A)
- If basal insulin is required, consider fixed-ratio insulin/GLP-1RA combinations (A)

Overall, it is the role of the primary care physician to view the patient as a whole. To this end, patients with T2D at high cardiovascular risk should also be assessed and treated for non-diabetes-related risk factors such as smoking cessation, dyslipidaemia and hypertension.

5.9. Elderly/frail patients

Due to the changing demographics in many countries, as well as the progressive nature of T2D, increasing numbers of patients with diabetes are elderly [188]. In addition, elderly patients are at greater risk of developing T2D complications due to longer duration of disease [188]. Increasing physical and mental frailty among the older population with T2D can render them more vulnerable to diabetes-related complications as well [189].

Quality of life should be a priority focus for patients who are elderly/frail. Stringent glycaemic targets are unlikely to be appropriate in this population due to the reduced life expectancy in which to accrue microvascular benefits, and because of the increased risk of hypoglycaemia [190]. Polypharmacy is also challenging for patients who may be experiencing cognitive decline or limited independence, necessitating simple glucose-lowering regimens [189]. That said, poor glycaemic control is a risk factor for sarcopenia, which is a major contributor to age-related frailty [191]. This may be part of what drives the 'obesity paradox,' the epidemiological finding that higher body mass index is related to improved survival in patients who do suffer an adverse cardiovascular event [192]. Quality of life is also negatively affected by such short-term symptoms of hyperglycaemia as recurrent cystitis, mycosis, itching, drowsiness, nocturia and increasing incontinency [193,194]. Defining adequate glycaemic control should include consideration of these issues, which may increase a patient's dependence on caregivers. Diabetes management in the elderly/frail population must balance treatment-related safety, personalised quality of life and adequate glycaemic control [3].

Evidence in support of individual treatments in elderly/frail populations is somewhat limited, though treatment guidelines have been formulated for this population [195,196].

If possible, multiple daily injectable treatments should be avoided in this population. Insulin must be prescribed cautiously, and most SUs should also be avoided due to increased risk of hypoglycaemia. If insulin is to be used, care should be taken to choose a treatment which reduces this risk [197]. When frailty is associated with weight loss that adversely affects health, treatments that further decrease weight may not be appropriate. Physicians should also consider assessing executive function of the patient as part of deciding on therapeutic strategy. Adherence to medication should be regularly assessed in elderly patients and regimens simplified as needed. In patients with cognitive impairments, treatments with once-weekly dosing, such as some long-acting GLP-1RAs, could be a good option to facilitate adherence as they can be administered conveniently by caregivers. Medications such as metformin that are taken more than once per day may not be appropriate for patients who struggle with adherence. SGLT2is should also be used with caution in frail patients.

DPP-4is can be important treatment options in the elderly/frail population, as they are well-tolerated with few side effects and associated with only modest HbA_{1c} reductions without increased risk of hypoglycaemia [198].

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Box 8: Treatment recommendations for elderly/frail patients

- Avoid stringent glycaemic targets that increase risk of hypoglycaemia (E)
- Metformin as first-line therapy if tolerated and not contraindicated (A)
- DPP-4i is a safe and easy to use option (A)
- Assess adherence and avoid multiple daily injectable medications when possible (E)

6. Conclusions

Recent years have seen an explosion of new treatment options for T2D, and while detailed guidelines exist to guide specialists in the nuances of treating T2D, few guidelines are targeted to help the primary care physicians navigate the growing number of options. This position statement has been designed to provide practical advice to primary care physicians globally to give the best possible care to their full range of patients with T2D.

The author group used a consensus approach to arrive at the specific treatment recommendations for patients with T2D in various categories of comorbidity. A simple but evidence-based scheme to stratify for cardiovascular risk in patients with T2D has been proposed (Box 2). Specific recommendations are given for patients with very high cardiovascular risk (including those with ASCVD, HF and CKD), for patients with high cardiovascular risk, and for elderly/frail patients. These recommendations have also been distilled down to a visual tool (Fig. 1) to further aid the busy primary care physician.

CVD is one of the most prevalent comorbidities causally associated with T2D and is the primary reason for mortality in these patients [58]. A wealth of data exists and is still being generated on how to minimise CV risk and other complications in patients with T2D. Navigating the data associated with the myriad of available treatment options can be daunting and necessitates the synthesis of easy-to-use treatment guidelines. Despite the extensive specialist-generated literature, more research is required specifically on the outcomes of the majority of patients with T2D treated in primary care. Primary care physicians, as the first point of contact in the healthcare system, represent the 'front lines' of T2D care and are uniquely placed in a continuity of care setting to take a patient-centred, whole-patient approach to T2D management [199].

Conflict of interest

SS has received consultancy and speaker fees from Amgen, Boehringer Ingelheim, Napp Pharmaceuticals, Novartis and Roche; advisory board, consultancy and speaker fees from AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi; and trial grant funding from AstraZeneca, Janssen Pharmaceutica, Sanofi and Servier Laboratories. XC has received consultancy and speaker fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche and Sanofi; and grant funding from AstraZeneca, Boehringer Ingelheim, Novartis and Sanofi. SB has received advisory board and speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen Pharmaceutica and Novo Nordisk; advisory board fees from Abbott Laboratories, Merck Sharp & Dohme, Sanofi and Xeris Pharmaceuticals; and speaker fees from Eli Lilly. SBH has received advisory board and consultancy fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen Pharmaceutica, Merck, Novo Nordisk and Sanofi. SJ received speaker fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi. MM-C has received fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi; and grant funding from AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme and Sanofi. AMJN has received speaker fees from Becton Dickinson; and advisory board feed from Sanofi. PT has received advisory board, consultancy and speaker fees from Eli Lilly; advisory board and consultancy fees from Boehringer Ingelheim and advisory board fees from Novo Nordisk. KK has received advisory board, consultancy and speaker fees from Novo Nordisk and Sanofi; consultancy and speaker fees from Berlin Chemie, Boehringer Ingelheim, Novartis, Novo Nordisk, Roche, Sanofi and Servier Laboratories; and grant funding from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi and Servier Laboratories.

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References

[1] S.E. Inzucchi, R.M. Bergenstal, J.B. Buse, et al., Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetes Care 35 (2012) 1364–1379, http://dx.doi.org/10.2337/dc12-0413.
[2] T. Bodenheimer, E.H. Wagner, K. Grumbach, Improving primary care for patients with chronic illness: the chronic care model, part 2, JAMA 288 (2002) 1909–1914, http://dx.doi.org/10.1001/jama.288.15.1909.
[3] C.E. Hambling, K. Khunti, X. Cos, et al., Factors influencing safe glucose-lowering in older adults with type 2 diabetes: A PeRsOn-centred ApproaCh To IndiVidualisEd (PROACTIVE) glycemic goals for older people: a position statement of primary care diabetes Europe, Primary Care Diabetes 13 (2019) 330–352, http://dx.doi.org/10.1016/j.pcd.2018.12.005.
[4] Diabetes in Europe – Policy Puzzle, European Coalition for Diabetes, 2014. https://www.fend.org/sites/fend.org/files/ECD-PP4finalweb.pdf (accessed 06.08.19).
[5] International Diabetes Federation, IDF Diabetes Atlas, eighth edition, International Diabetes Federation, Brussels, Belgium, 2017.

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[6] K. Blaslov, F.S. Naranđa, I. Kruljac, I.P. Renar, Treatment approach to type 2 diabetes: Past, present and future, WJD 9 (2018) 209–219, http://dx.doi.org/10.4239/wjd.v9.i12.209.
[7] K. Khunti, S. Seidu, Therapeutic inertia and the legacy of dysglycemia on the microvascular and macrovascular complications of diabetes, Diabetes Care 42 (2019) 349–351, http://dx.doi.org/10.2337/dci18-0030.
[8] E.W. Gregg, N. Sattar, M.K. Ali, The changing face of diabetes complications, Lancet Diabetes Endocrinol. 4 (2016) 537–547, http://dx.doi.org/10.1016/S2213-8587(16)30010-9.
[9] K.M.V. Narayan, U.P. Gujral, Evidence tips the scale toward screening for hyperglycemia, Diabetes Care 38 (2015) 1399–1401, http://dx.doi.org/10.2337/dc15-0856.
[10] T.R. Einarson, A. Acs, C. Ludwig, U.H. Panton, Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017, Cardiovasc. Diabetol. 17 (2018) 83, http://dx.doi.org/10.1186/s12933-018-0728-6.
[11] M.J. Davies, D.A. D'Alessio, J. Fradkin, et al., Management of hyperglycemia in Type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetes Care 41 (2018) 2669–2701, http://dx.doi.org/10.2337/dci18-0033.
[12] M.J. Davies, D.A. D'Alessio, J. Fradkin, et al., Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia 61 (2018) 2461–2498, http://dx.doi.org/10.1007/s00125-018-4729-5.
[13] J. Reeve, T. Blakeman, G.K. Freeman, et al., Generalist solutions to complex problems: generating practice-based evidence – the example of managing multi-morbidity, BMC Fam. Pract. 14 (2013) 112, http://dx.doi.org/10.1186/1471-2296-14-112.
[14] B. Rushforth, C. McCrorie, L. Glidewell, et al., Barriers to effective management of type 2 diabetes in primary care: qualitative systematic review, Br. J. Gen. Pract. 66 (2016) e114–e127, http://dx.doi.org/10.3399/bjgp16X683509.
[15] G.E.H.M. Rutten, H.A. van Vugt, I. de Weerdt, E. de Koning, Implementation of a structured diabetes consultation model to facilitate a person-centered approach: results from a Nationwide Dutch Study, Diabetes Care (2018) dc171194, http://dx.doi.org/10.2337/dc17-1194.
[16] H.A. van Vugt, E.J.P. de Koning, G.E.H.M. Rutten, Association between person and disease related factors and the planned diabetes care in people who receive person-centered type 2 diabetes care: an implementation study, PLOS ONE 14 (2019) e0219702, http://dx.doi.org/10.1371/journal.pone.0219702.
[17] A. Norful, G. Martsolf, K. de Jacq, L. Poghosyan, Utilization of registered nurses in primary care teams: a systematic review, Int. J. Nurs. Stud. 74 (2017) 15–23, http://dx.doi.org/10.1016/j.ijnurstu.2017.05.013.
[18] D. Jeavons, Patients with poorly controlled diabetes in primary care: healthcare clinicians' beliefs and attitudes, Postgrad. Med. J. 82 (2006) 347–350, http://dx.doi.org/10.1136/pgmj.2005.039545.
[19] S. Seidu, M.J. Davies, A. Farooqi, K. Khunti, Integrated primary care: is this the solution to the diabetes epidemic? Diabetes Med. 34 (2017) 748–750, http://dx.doi.org/10.1111/dme.13348.
[20] S. Khunti, K. Khunti, S. Seidu, Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia, Therap. Adv. Endocrinol. 10 (2019), http://dx.doi.org/10.1177/2042018819844694.
[21] K. Khunti, M.B. Gomes, S. Pocock, et al., Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review, Diabetes Obes. Metab. 20 (2018) 427–437, http://dx.doi.org/10.1111/dom.13088.
[22] R. van Bruggen, K. Gorter, R. Stolk, et al., Clinical inertia in general practice: widespread and related to the outcome of diabetes care, Fam Pract 26 (2009) 428–436, http://dx.doi.org/10.1093/fampra/cmp053.
[23] M.A. Stone, G. Charpentier, K. Doggen, et al., Quality of care of people with type 2 diabetes in eight European countries: Findings from the Guideline Adherence to Enhance Care (GUIDANCE) study, Diabetes Care 36 (2013) 2628–2638, http://dx.doi.org/10.2337/dc12-1759.
[24] N. Zhang, X. Yang, X. Zhu, et al., Type 2 diabetes mellitus unawareness, prevalence, trends and risk factors: National Health and Nutrition Examination Survey (NHANES) 1999–2010, J. Int. Med. Res. 45 (2017) 594–609, http://dx.doi.org/10.1177/0300060517693178.
[25] T. Santos Cavaiola, Y. Kiriakov, T. Reid, Primary care management of patients with type 2 diabetes: overcoming inertia and advancing therapy with the use of injectables, Clin. Therap. 41 (2019) 352–367, http://dx.doi.org/10.1016/j.clinthera.2018.11.015.
[26] K. Khunti, A. Ceriello, X. Cos, C. De Block, Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: a meta-analysis, Diabetes Res. Clin. Pract. 137 (2018) 137–148, http://dx.doi.org/10.1016/j.diabres.2017.12.004.
[27] R. van Bruggen, K. Gorter, R.P. Stolk, et al., Refill adherence and polypharmacy among patients with type 2 diabetes in general practice, Pharmacoepidemiol. Drug Saf. 18 (2009) 983–991, http://dx.doi.org/10.1002/pds.1810.
[28] S.J. Griffin, K. Borch-Johnsen, M.J. Davies, et al., Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial, Lancet 378 (2011) 156–167, http://dx.doi.org/10.1016/S0140-6736(11)60698-3.
[29] S.J. Griffin, G.E.H.M. Rutten, K. Khunti, et al., Long-term effects of intensive multifactorial therapy in individuals with screen-detected type 2 diabetes in primary care: 10-year follow-up of the ADDITION-Europe cluster-randomised trial, Lancet Diabetes Endocrinol. 7 (2019) 925–937, http://dx.doi.org/10.1016/S2213-8587(19)30349-3.
[30] X. Cos, Understanding the Primary Care Landscape in Europe, 2019.
[31] K. Khunti, S. Seidu, Diabetes research in primary care: fiction, reality or essential? Diabetes Med. 35 (2018) 832–834, http://dx.doi.org/10.1111/dme.13638.
[32] C. Saunders, C.D. Byrne, B. Guthrie, et al., External validity of randomized controlled trials of glycaemic control and vascular disease: how representative are participants? Diabetes Med. 30 (2013) 300–308, http://dx.doi.org/10.1111/dme.12047.
[33] A. McGovern, M. Feher, N. Munro, S. de Lusignan, Sodium-glucose cotransporter 2 (SGLT2) inhibitor: comparing trial data and real-world use, Diabetes Ther. 8 (2017) 365–376, http://dx.doi.org/10.1007/s13300-017-0254-7.
[34] K.I. Birkeland, J. Bodegard, A. Norhammar, et al., How representative of a general type 2 diabetes population are patients included in cardiovascular outcome trials with SGLT2 inhibitors? A large European observational study, Diabetes Obes. Metab. 21 (2019) 968–974, http://dx.doi.org/10.1111/dom.13612.
[35] E.T. Wittbrodt, J.M. Eudicone, K.F. Bell, et al., Eligibility varies among the 4 sodium-glucose cotransporter-2 inhibitor cardiovascular outcomes trials: implications for the general type 2 diabetes US population, Am. J. Manag. Care 24 (2018) S138–S145.
[36] S.C. Bain, A. Bakhai, M. Evans, et al., Pharmacological treatment for Type 2 diabetes integrating findings from cardiovascular outcome trials: an expert consensus in the UK, Diabetic Medicine. (n.d.). https://doi.org/10.1111/dme.14058.
[37] F. Cosentino, P.J. Grant, V. Aboyans, et al., 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, Euro. Heart J. (2019) ehz486, http://dx.doi.org/10.1093/eurheartj/ehz486.
[38] International Diabetes Federation, IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care, 2017, https://www.idf.org/e-library/guidelines/128-idf-clinical-practice-recommendations-for-managing-type-2-diabetes-in-primary-care.html (accessed 14.08.19).
[39] K. Vella, Use of consensus development to establish national research priorities in critical care, BMJ 320 (2000) 976–980, http://dx.doi.org/10.1136/bmj.320.7240.976.
[40] WHOCC – ATC/DDD Index, (n.d.). https://www.whocc.no/atc_ddd_index/ (accessed 17.10.19).
[41] W. Polonsky, R. Henry, Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors, PPA 10 (2016) 1299–1307, http://dx.doi.org/10.2147/PPA.S1068.21.
[42] R. Rodriguez-Gutierrez, M.R. Gionfriddo, N.S. Ospina, et al., Shared decision making in endocrinology: present and future directions, Lancet Diabetes Endocrinol 4 (2016) 706–716, http://dx.doi.org/10.1016/S2213-8587(15)0046.8-4.
[43] S.M. Marshall, 60 years of metformin use: a glance at the past and a look to the future, Diabetologia 60 (2017) 1561–1565, http://dx.doi.org/10.1007/s00125-017-4343-y.
[44] UK Prospective Diabetes Study (UKPDS) Group, Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34), Lancet 352 (1998) 854–865, http://dx.doi.org/10.1016/S0140-6736(98)07037-8.
[45] Scottish Intercollegiate Guidelines Network (SIGN), pharmacological management of glycaemic control in people with type 2 diabetes, 2019. https://www.sign.ac.uk/assets/sign154.pdf (accessed 09.08.19).
[46] S.J. Griffin, J.K. Leaver, G.J. Irving, Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes, Diabetologia 60 (2017) 1620–1629, http://dx.doi.org/10.1007/s00125-017-4337-9.
[47] T. Dujic, K. Zhou, L.A. Donnelly, et al., Association of organic cation transporter 1 with intolerance to metformin in type 2 diabetes: a GoDARTS study, Diabetes 64 (2015) 1786–1793, http://dx.doi.org/10.2337/db14-1388.
[48] D.R. Matthews, P.M. Paldánius, P. Proot, et al., Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial, Lancet (2019), http://dx.doi.org/10.1016/S0140-6736(19)3213.1-2.
[49] M.A. Abdul-Ghani, C. Puckett, C. Triplitt, et al., Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial, Diabetes Obes. Metab. 17 (2015) 268–275, http://dx.doi.org/10.1111/dom.12417.
[50] R.R. Holman, S.K. Paul, M.A. Bethel, et al., 10-year follow-up of intensive glucose control in type 2 diabetes, N. Engl. J. Med. 359 (2008) 1577–1589, http://dx.doi.org/10.1056/NEJMoa0806470.
[51] N. Laiteerapong, S.A. Ham, Y. Gao, et al., The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (The Diabetes & Aging Study), Diabetes Care 42 (2019) 416–426, http://dx.doi.org/10.2337/dc17-1144.
[52] P.D. Reaven, N.V. Emanuele, W.L. Wiitala, et al., Intensive glucose control in patients with Type 2 diabetes — 15-year follow-up, N. Engl. J. Med. (2019), http://dx.doi.org/10.1056/NEJMoa.1806.802.

Please cite this article in press as: S. Seidu, et al., A disease state approach to the pharmacological management of Type 2 diabetes in primary care: A position statement by Primary Care Diabetes Europe, Prim. Care Diab. (2020), https://doi.org/10.1016/j.pcd.2020.05.004

[53] A.N. Goudswaard, R.P. Stolk, H.W. de Valk, G.E.H.M. Rutten, Improving glycaemic control in patients with Type 2 diabetes mellitus without insulin therapy, Diabetes Med. 20 (2003) 540–544, http://dx.doi.org/10.1046/j.1464-5491.2003.00980.x.
[54] World Health Organization, Cardiovascular diseases (CVDs), 2017, https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed 08.08.19).
[55] K. Khunti, M. Kosiborod, K.K. Ray, Legacy benefits of blood glucose, blood pressure and lipid control in individuals with diabetes and cardiovascular disease: time to overcome multifactorial therapeutic inertia? Diabetes Obes. Metab. 20 (2018) 1337–1341, http://dx.doi.org/10.1111/dom.13243.
[56] S.P. Karunathilake, G.U. Ganegoda, Secondary prevention of cardiovascular diseases and application of technology for early diagnosis, BioMed Res. Int. 2018 (2018) 1–9, http://dx.doi.org/10.1155/2018/5767864.
[57] D.M. Lloyd-Jones, L.T. Braun, C.E. Ndumele, et al., Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the american heart association and American college of cardiology, J. Am. Coll. Cardiol. 73 (2019) 3153–3167, http://dx.doi.org/10.1016/j.jacc.2018.11.005.
[58] American Diabetes Association, 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2019, Diabetes Care 42 (2019) S103–S123, http://dx.doi.org/10.2337/dc19-S010.
[59] J.B. Young, M. Gauthier-Loiselle, R.A. Bailey, et al., Development of predictive risk models for major adverse cardiovascular events among patients with type 2 diabetes mellitus using health insurance claims data, Cardiovasc. Diabetol. 17 (2018) 118, http://dx.doi.org/10.1186/s12933-018-0759-z.
[60] C.J. Currie, E.R. Berni, T.R. Berni, et al., Major adverse cardiovascular events in people with chronic kidney disease in relation to disease severity and diabetes status, PLOS ONE 14 (2019), http://dx.doi.org/10.1371/journal.pone.0221.044.
[61] C. Ke, B.R. Shah, A.O. Luk, et al., Cardiovascular outcomes trials in type 2 diabetes: Time to include young adults, Diabetes Obes, Metabol, (n.d.). https://doi.org/10.1111/dom.13874.
[62] T.A. Hillier, K.L. Pedula, Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth, Diabetes Care 26 (2003) 2999–3005, http://dx.doi.org/10.2337/diacare.26.11.2999.
[63] I. Conget, M. Gimenez, Glucose control and cardiovascular disease: is it important? No, Diabetes Care 32 (2009) S334–S336, http://dx.doi.org/10.2337/dc09-S334.
[64] The Action to Control Cardiovascular Risk in Diabetes Study Group, Effects of intensive glucose lowering in type 2 diabetes, N. Engl. J. Med. 358 (2008) 2545–2559, http://dx.doi.org/10.1056/NEJMoa0802743.
[65] R. Boussageon, T. Bejan-Angoulvant, M. Saadatian-Elahi, et al., Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials, BMJ 343 (2011) d4169, http://dx.doi.org/10.1136/bmj.d.4169.
[66] M. Hanefeld, B.M. Frier, F. Pistrosch, Hypoglycemia and cardiovascular risk: is there a major link? Diabetes Care 39 (2016) S205–S209, http://dx.doi.org/10.2337/dcS15-3014.
[67] F.M. Turnbull, C. Abraira, R.J. Anderson, et al., Intensive glucose control and macrovascular outcomes in type 2 diabetes, Diabetologia 52 (2009) 2288–2298, http://dx.doi.org/10.1007/s00125-009-1470-0.
[68] K.K. Ray, S.R.K. Seshasai, S. Wijesuriya, et al., Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials, Lancet 373 (2009) 1765–1772, http://dx.doi.org/10.1016/S0140-6736(09)6069.7-8.
[69] M.M. Lawes Carlene, D.A. Bennett, V.L. Feigin, A. Rodgers, Blood pressure and stroke, Stroke 35 (2004) 776–785, http://dx.doi.org/10.1161/01.STR.0000116869.6477.1.5A.
[70] S.P. Marso, G.H. Daniels, K. Brown-Frandsen, et al., Liraglutide and cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med. 375 (2016) 311–322, http://dx.doi.org/10.1056/NEJMoa.1603.827.
[71] S.P. Marso, S.C. Bain, A. Consoli, et al., Semaglutide and cardiovascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 375 (2016) 1834–1844, http://dx.doi.org/10.1056/NEJMoa.1607141.
[72] M. Husain, A.L. Birkenfeld, M. Donsmark, et al., Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 381 (2019) 841–851, http://dx.doi.org/10.1056/NEJMoa.1901.118.
[73] K. Dahl-Jørgensen, O. Brinchmann-Hansen, K.F. Hanssen, et al., Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study, Br. Med. J. (Clin. Res. Ed.) 290 (1985) 811–815, http://dx.doi.org/10.1136/bmj.290.6471.811.
[74] A.F. Hernandez, J.B. Green, S. Janmohamed, et al., Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial, Lancet 392 (2018) 1519–1529, http://dx.doi.org/10.1016/S0140-6736(18)3226.1-X.
[75] H.C. Gerstein, H.M. Colhoun, G.R. Dagenais, et al., Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial, Lancet 394 (2019) 121–130, http://dx.doi.org/10.1016/S0140-6736(19)3114.9-3.
[76] M.A. Pfeffer, B. Claggett, R. Diaz, et al., Lixisenatide in patients with type 2 diabetes and acute coronary syndrome, N. Engl. J. Med. 373 (2015) 2247–2257, http://dx.doi.org/10.1056/NEJMoa.1509.225.
[77] R.R. Holman, M.A. Bethel, R.J. Mentz, et al., Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med. 377 (2017) 1228–1239, http://dx.doi.org/10.1056/NEJMoa.1612.917.
[78] M.A. Bethel, R.A. Patel, P. Merrill, et al., Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis, Lancet Diabetes Endocrinol. 6 (2018) 105–113, http://dx.doi.org/10.1016/S2213-8587(17)3041.2-6.
[79] B. Zinman, C. Wanner, J.M. Lachin, et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med. 373 (2015) 2117–2128, http://dx.doi.org/10.1056/NEJMoa.1504.720.
[80] B. Neal, V. Perkovic, K.W. Mahaffey, et al., Canagliflozin and cardiovascular and renal events in type 2 diabetes, N. Engl. J. Med. 377 (2017) 644–657, http://dx.doi.org/10.1056/NEJMoa.1611.925.
[81] S.D. Wiviott, I. Raz, M.P. Bonaca, et al., Dapagliflozin and cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med. 380 (2019) 347–357, http://dx.doi.org/10.1056/NEJMoa.1812.389.
[82] T.A. Zelniker, S.D. Wiviott, I. Raz, et al., SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials, Lancet 393 (2019) 31–39, http://dx.doi.org/10.1016/S0140-6736(18)3259.0-X.
[83] S.P. Marso, D.K. McGuire, B. Zinman, et al., Efficacy and safety of degludec versus glargine in type 2 diabetes, N. Engl. J. Med. 377 (2017) 723–732, http://dx.doi.org/10.1056/NEJMoa.1615.692.
[84] A. Llano, G. McKay, The treatment of type 2 diabetes in heart failure, Pract. Diabetes 35 (2018) 123–126, http://dx.doi.org/10.1002/pdi.2178.
[85] R.M. Cubbon, B. Adams, A. Rajwani, et al., Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology, Diabetes Vasc. Dis. Res. 10 (2013) 330–336, http://dx.doi.org/10.1177/1479164112471064.
[86] M. Lehrke, N. Marx, Diabetes mellitus and heart failure, Am. J. Med. 130 (2017) S40–S50, http://dx.doi.org/10.1016/j.amjmed.2017.04.010.
[87] Y. Wang, T. Negishi, K. Negishi, T.H. Marwick, Prediction of heart failure in patients with type 2 diabetes mellitus- a systematic review and meta-analysis, Diabetes Res. Clin. Pract. 108 (2015) 55–66, http://dx.doi.org/10.1016/j.diabres.2015.01.011.
[88] C.A. Lawson, P.W. Jones, L. Teece, et al., Association between type 2 diabetes and all-cause hospitalization and mortality in the UK general heart failure population: stratification by diabetic glycemic control and medication intensification, J. Am. Coll. Cardiol. HF 6 (2017) 18–26, http://dx.doi.org/10.1016/j.jchf.2017.08.020.
[89] C.A. Lawson, F. Zaccardi, I. Squire, et al., 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study, Lancet Public Health 4 (2019) e406–e420, http://dx.doi.org/10.1016/S2468-2667(19)3010.8-2.
[90] D. Fitchett, B. Zinman, C. Wanner, et al., Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME ® trial, Eur. Heart J. 37 (2016) 1526–1534, http://dx.doi.org/10.1093/eurheartj/ehv728.
[91] K. Rådholm, G. Figtree, V. Perkovic, et al., Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS program, Circulation 138 (2018) 458–468, http://dx.doi.org/10.1161/CIRCULATIONAHA.118.0342.22.
[92] J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, et al., Dapagliflozin in patients with heart failure and reduced ejection fraction, N. Engl. J. Med. (2019), http://dx.doi.org/10.1056/NEJMoa.1911303.
[93] M. Kosiborod, M.A. Cavender, A.Z. Fu, et al., Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs, Circulation 136 (2017) 249–259, http://dx.doi.org/10.1161/CIRCULATIONAHA.117.0291.90.
[94] A.J. Scheen, Does lower limb amputation concern all SGLT2 inhibitors? Nat. Rev. Endocrinol. 14 (2018) 326–328, http://dx.doi.org/10.1038/s41574-018-0001-9.
[95] M. Monami, C. Nardini, E. Mannucci, Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials: SGLT-2 inhibitors in type 2 diabetes, Diabetes Obes. Metab. 16 (2014) 457–466, http://dx.doi.org/10.1111/dom.1224.4.
[96] Janssen Pharmaceuticals, Inc., Invokana (canagliflozin) Prescribing Information, 2013, http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf (accessed 16.08.19).
[97] Bristol-Myers Squibb Company, Farxiga (dapagliflozin) Prescribing Information, 2014, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf (accessed 16.08.19).
[98] Boehringer Ingelheim Pharmaceuticals, Jardiance (empagliflozin) Prescribing Information, 2018, https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf (accessed 16.08.19).
[99] J.A. Dormandy, B. Charbonnel, D.J.A. Eckland, et al., Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial, Lancet 366 (2005) 1279–1289, http://dx.doi.org/10.1016/S0140-6736(05)6752.8-9.
[100] M. de Jong, H.B. van der Worp, Y. van der Graaf, et al., Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials, Cardiovasc. Diabetol. 16 (2017) 134, http://dx.doi.org/10.1186/s12933-017-0617-4.
[101] O. Vaccaro, M. Masulli, A. Nicolucci, et al., Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a

Please cite this article in press as: S. Seidu, et al., A disease state approach to the pharmacological management of Type 2 diabetes in primary care: A position statement by Primary Care Diabetes Europe, Prim. Care Diab. (2020), https://doi.org/10.1016/j.pcd.2020.05.004

randomised multicentre trial, Lancet Diabetes Endocrinol. 5 (2017) 887–897, http://dx.doi.org/10.1016/S2213-8587(17)3031.7-0.
[102] M. Packer, Worsening heart failure during the use of DPP-4 inhibitors, JACC: Heart Fail. 6 (2018) 445–451, http://dx.doi.org/10.1016/j.jchf.2017.12.016.
[103] B.M. Scirica, E. Braunwald, I. Raz, et al., Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial, Circulation 130 (2014) 1579–1588, http://dx.doi.org/10.1161/CIRCULATIONAHA.114.0103.89.
[104] F. Zannad, C.P. Cannon, W.C. Cushman, et al., Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial, Lancet 385 (2015) 2067–2076, http://dx.doi.org/10.1016/S0140-6736(14)6222.5-X.
[105] J.B. Green, M.A. Bethel, P.W. Armstrong, et al., Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med. 373 (2015) 232–242, http://dx.doi.org/10.1056/NEJMoa.1501.352.
[106] J. Rosenstock, V. Perkovic, O.E. Johansen, et al., Effect of Linagliptin vs Placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial, JAMA 321 (2019) 69–79, http://dx.doi.org/10.1001/jama.2018.1826.9.
[107] R.A. DeFronzo, C.R. Cooke, R. Andres, et al., The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man, J. Clin. Invest. 55 (1975) 845–855, http://dx.doi.org/10.1172/JCI.1079.96.
[108] P. Raskin, M. Rendell, M.C. Riddle, et al., Rosiglitazone clinical trials study group. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes, Diabetes Care 24 (2001) 1226–1232, http://dx.doi.org/10.2337/diacare.24.7.1226.
[109] F. Cosmi, L. Shen, M. Magnoli, et al., Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes, Euro. J. Heart Fail. 20 (2018) 888–895, http://dx.doi.org/10.1002/ejhf.1146.
[110] R.Z. Alicic, M.T. Rooney, K.R. Tuttle, Diabetic kidney disease: challenges, progress, and possibilities, CJASN 12 (2017) 2032–2045, http://dx.doi.org/10.2215/CJN.11491116.
[111] M. Brownlee, The pathobiology of diabetic complications: a unifying mechanism, Diabetes 54 (2005) 1615–1625, http://dx.doi.org/10.2337/diabetes.54.6.1615.
[112] M. Davies, S. Chatterjee, K. Khunti, The treatment of type 2 diabetes in the presence of renal impairment: what we should know about newer therapies, Clin. Pharmacol. 8 (2016) 61–81, http://dx.doi.org/10.2147/CPAA.S.8200.8.
[113] American Diabetes Association, 11. Microvascular complications and foot care: standards of medical care in diabetes—2019, Diabetes Care 42 (2019) S124–S138, http://dx.doi.org/10.2337/dc19-S011.
[114] J.K. Duong, D.M. Roberts, T.J. Furlong, et al., Metformin therapy in patients with chronic kidney disease, Diabetes Obes. Metabol. 14 (2012) 963–965, http://dx.doi.org/10.1111/j.1463-1326.2012.0161.7.x.
[115] V. Perkovic, H.L. Heerspink, J. Chalmers, et al., Intensive glucose control improves kidney outcomes in patients with type 2 diabetes, Kidney Int. 83 (2013) 517–523, http://dx.doi.org/10.1038/ki.2012.401.
[116] M.G. Wong, V. Perkovic, J. Chalmers, et al., Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON, Diabetes Care 39 (2016) 694–700, http://dx.doi.org/10.2337/dc15-2322.
[117] I. Ioannidis, Diabetes treatment in patients with renal disease: is the landscape clear enough? World J. Diabetes 5 (2014) 651–658, http://dx.doi.org/10.4239/wjd.v5.i5.651.
[118] S. Colagiuri, D. Matthews, L.A. Leiter, et al., The place of gliclazide MR in the evolving type 2 diabetes landscape: a comparison with other sulfonylureas and newer oral antihyperglycemic agents, Diabetes Res. Clin. Pract. 143 (2018) 1–14, http://dx.doi.org/10.1016/j.diabres.201805.028.
[119] J.J. Neumiller, I.B. Hirsch, Management of hyperglycemia in diabetic kidney disease, Diabetes Spectrum. 28 (2015) 214–219, http://dx.doi.org/10.2337/diaspect.28.3.214.
[120] L.A. Sloan, Review of glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus in patients with chronic kidney disease and their renal effects, J. Diabetes (2019), http://dx.doi.org/10.1111/1753-0407.1296.9.
[121] V. Vallon, S.C. Thomson, Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition, Diabetologia 60 (2017) 215–225, http://dx.doi.org/10.1007/s00125-016-4157-3.
[122] C. Wanner, S.E. Inzucchi, J.M. Lachin, et al., Empagliflozin and progression of kidney disease in type 2 diabetes, N. Engl. J. Med. 375 (2016) 323–334, http://dx.doi.org/10.1056/NEJMoa.1515920.
[123] V. Perkovic, M.J. Jardine, B. Neal, et al., Canagliflozin and renal outcomes in type 2 diabetes and nephropathy, N. Engl. J. Med. 380 (2019) 2295–2306, http://dx.doi.org/10.1056/NEJMoa.1811.744.
[124] O. Mosenzon, S.D. Wiviott, A. Cahn, et al., Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial, Lancet Diabetes Endocrinol. 7 (2019) 606–617, http://dx.doi.org/10.1016/S2213-8587(19)3018.0-9.
[125] A. Menke, S. Casagrande, L. Geiss, C.C. Cowie, Prevalence of and trends in diabetes among adults in the United States, 1988–2012, JAMA 314 (2015) 1021–1029, http://dx.doi.org/10.1001/jama.2015.10029.
[126] The GBD 2015 Obesity Collaborators, Health effects of overweight and obesity in 195 countries over 25 years, N. Engl. J. Med. 377 (2017) 13–27, http://dx.doi.org/10.1056/NEJMoa1614362.
[127] M.-A. Cornier, D. Dabelea, T.L. Hernandez, et al., The metabolic syndrome, Endocr. Rev. 29 (2008) 777–822, http://dx.doi.org/10.1210/er.2008-0024.
[128] O.T. Hardy, M.P. Czech, S. Corvera, What causes the insulin resistance underlying obesity? Curr. Opin. Endocrinol. Diabetes Obes. 19 (2012) 81–87, http://dx.doi.org/10.1097/MED.0b013e.3283.514e13.
[129] E. Ahlqvist, P. Storm, A. Käräjämäki, et al., Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables, Lancet Diabetes Endocrinol. 6 (2018) 361–369, http://dx.doi.org/10.1016/S2213-8587(18)3005.1-2.
[130] S.M. Haffner, S. Lehto, T. Rönnemaa, et al., Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction, N. Engl. J. Med. 339 (1998) 229–234, http://dx.doi.org/10.1056/NEJM199807233390.404.
[131] J.D. Newman, A.Z. Schwartzbard, H.S. Weintraub, et al., Primary prevention of cardiovascular disease in diabetes mellitus, J. Am. Coll. Cardiol. 70 (2017) 883–893, http://dx.doi.org/10.1016/j.jacc.2017.07.001.
[132] S. Zoungas, A. Patel, J. Chalmers, et al., Severe hypoglycemia and risks of vascular events and death, N. Engl. J. Med. 363 (2010) 1410–1418, http://dx.doi.org/10.1056/NEJMoa.1003.795.
[133] F. Giorgino, P.D. Home, J. Tuomilehto, Glucose control and vascular outcomes in type 2 diabetes: is the picture clear? Diabetes Care 39 (2016) S187–S195, http://dx.doi.org/10.2337/dcS15-3023.
[134] D. Sherifali, K. Nerenberg, E. Pullenayegum, et al., The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis, Diabetes Care 33 (2010) 1859–1864, http://dx.doi.org/10.2337/dc09-1727.
[135] S.E. Kahn, S.M. Haffner, M.A. Heise, et al., Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy, N. Engl. J. Med. 355 (2006) 2427–2443, http://dx.doi.org/10.1056/NEJMoa.066224.
[136] M. Nauck, A. Frid, K. Hermansen, et al., Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study, Diabetes Obes. Metab. 15 (2013) 204–212, http://dx.doi.org/10.1111/dom.1201.2.
[137] M. Ridderstråle, J. Rosenstock, K.R. Andersen, et al., Empagliflozin compared with glimepiride in metformin-treated patients with type 2 diabetes: 208-week data from a masked randomized controlled trial, Diabetes Obes. Metab. 20 (2018) 2768–2777, http://dx.doi.org/10.1111/dom.1345.7.
[138] D. Varvaki Rados, L. Catani Pinto, L. Reck Remonti, et al., The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials, PLoS Med. 13 (2016), http://dx.doi.org/10.1371/journal.pmed.1001.992.
[139] J. Rosenstock, S.E. Kahn, O.E. Johansen, et al., Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial, JAMA 322 (2019) 1155–1166, http://dx.doi.org/10.1001/jama.2019.1377.2.
[140] UK Prospective Diabetes Study (UKPDS) Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), Lancet 352 (1998) 837–853.
[141] L.M. Pop, I. Lingvay, The infamous, famous sulfonylureas and cardiovascular safety: much ado about nothing? Curr. Diabetes Rep. 17 (2017) 124, http://dx.doi.org/10.1007/s11892-017-0954-4.
[142] A.D.B. Harrower, Efficacy of gliclazide in comparison with other sulphonylureas in the treatment of NIDDM, Diabetes Res. Clin. Pract. 14 (1991) S65–S67, http://dx.doi.org/10.1016/0168-8227(91)9001.0-B.
[143] S.E. Andersen, M. Christensen, Hypoglycaemia when adding sulphonylurea to metformin: a systematic review and network meta-analysis, Br. J. Clin. Pharmacol. 82 (2016) 1291–1302, http://dx.doi.org/10.1111/bcp.1305.9.
[144] ADVANCE Collaborative Group, A. Patel, S. MacMahon, et al., Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 358 (2008) 2560–2572, http://dx.doi.org/10.1056/NEJMoa.0802987.
[145] D.G. Dills, J. Schneider, Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study. Glimepiride/Glyburide Research Group, Horm. Metab. Res. 28 (1996) 426–429, http://dx.doi.org/10.1055/s-2007-9798.31.
[146] C.K. Chow, C. Ramasundarahettige, W. Hu, et al., Availability and affordability of essential medicines for diabetes across high-income, middle-income, and low-income countries: a prospective epidemiological study, Lancet Diabetes Endocrinol. 6 (2018) 798–808, http://dx.doi.org/10.1016/S2213-8587(18)3023.3-X.
[147] S.H. Simpson, J. Lee, S. Choi, et al., Mortality risk among sulfonylureas: a systematic review and network meta-analysis, Lancet Diabetes Endocrinol. 3 (2015) 43–51, http://dx.doi.org/10.1016/S2213-8587(14)7021.3-X.
[148] A.S. Gangji, T. Cukierman, H.C. Gerstein, et al., A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin, Diabetes Care 30 (2007) 389–394, http://dx.doi.org/10.2337/dc06-1789.
[149] D.R. Webb, M.J. Davies, J. Jarvis, et al., The right place for Sulphonylureas today: part of review the series: implications of recent CVOTs in Type 2 diabetes mellitus, Diabetes Res. Clin. Pract. (2019) 107836, http://dx.doi.org/10.1016/j.diabres.2019.1078.36.
[150] R. Guardado-Mendoza, A. Prioletta, L.M. Jiménez-Ceja, et al., The role of nateglinide and repaglinide, derivatives of meglitinide, in the treatment of type 2 diabetes mellitus, Arch. Med. Sci. 9 (2013) 936–943, http://dx.doi.org/10.5114/aoms.2013.3499.1.
[151] T.K. Schramm, G.H. Gislason, A. Vaag, et al., Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nation-

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wide study, Eur, Heart. J. 32 (2011) 1900–1908, http://dx.doi.org/10.1093/eurheartj/ehr077.
[152] G. Schernthaner, D.R. Matthews, B. Charbonnel, et al., Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial, J. Clin. Endocrinol. Metab. 89 (2004) 6068–6076, http://dx.doi.org/10.1210/jc.2003-0308.61.
[153] B. Charbonnel, G. Schernthaner, P. Brunetti, et al., Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes, Diabetologia 48 (2005) 1093–1104, http://dx.doi.org/10.1007/s00125-005-1751-1.
[154] J.P.H. van Wijk, E.J.P. de Koning, E.P. Martens, T.J. Rabelink, Thiazolidinediones and blood lipids in type 2 diabetes, Arterioscler. Thromb. Vasc. Biol. 23 (2003) 1744–1749, http://dx.doi.org/10.1161/01.ATV. 0000090521.25968.4D.
[155] A.M. Lincoff, K. Wolski, S.J. Nicholls, S.E. Nissen, Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials, JAMA 298 (2007) 1180–1188, http://dx.doi.org/10.1001/jama.298.10.1180.
[156] S.E. Nissen, S.J. Nicholls, K. Wolski, et al., Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial, JAMA 299 (2008) 1561–1573, http://dx.doi.org/10.1001/jama.299.13.1561.
[157] T. Mazzone, P.M. Meyer, S.B. Feinstein, et al., Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial, JAMA 296 (2006) 2572–2581, http://dx.doi.org/10.1001/jama.296.21.joc.6015.8.
[158] A.J. Sanyal, N. Chalasani, K.V. Kowdley, et al., Pioglitazone, vitamin e, or placebo for nonalcoholic steatohepatitis, N. Engl. J. Med. 362 (2010) 1675–1685, http://dx.doi.org/10.1056/NEJMoa.0907.929.
[159] P. Portillo, S. Yavuz, F. Bril, K. Cusi, Role of insulin resistance and diabetes in the pathogenesis and treatment of nonalcoholic fatty liver disease, Curr. Hepatol. Rep. 13 (2014) 159–170, http://dx.doi.org/10.1007/s11901-014-0229-3.
[160] R.W. Nesto, D. Bell, R.O. Bonow, et al., Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association, Diabetes Care 27 (2004) 256–263, http://dx.doi.org/10.2337/diacare.27.1.256.
[161] V. Fonseca, Effect of thiazolidinediones on body weight in patients with diabetes mellitus, Am. J. Med. 115 (Suppl 8A) (2003) 42S–48S, http://dx.doi.org/10.1016/j.amjmed.2003.09.005.
[162] D.J. Betteridge, Thiazolidinediones and fracture risk in patients with Type 2 diabetes, Diabetes Med. 28 (2011) 759–771, http://dx.doi.org/10.1111/j.1464-5491.2010.03187.x.
[163] J.D. Lewis, A. Ferrara, T. Peng, et al., Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study, Diabetes Care 34 (2011) 916–922, http://dx.doi.org/10.2337/dc10-1068.
[164] J.J. DiNicolantonio, J. Bhutani, J.H. O'Keefe, Acarbose: safe and effective for lowering postprandial hyperglycaemia and improving cardiovascular outcomes, Open Heart. 2 (2015), http://dx.doi.org/10.1136/openhrt-2015-0003.27.
[165] Q. Zhu, Y. Tong, T. Wu, et al., Comparison of the hypoglycemic effect of acarbose monotherapy in patients with type 2 diabetes mellitus consuming an Eastern or Western diet: a systematic meta-analysis, Clin. Ther. 35 (2013) 880–899, http://dx.doi.org/10.1016/j.clinthera.2013.03.020.
[166] J.-L. Chiasson, R.G. Josse, R. Gomis, et al., Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM trial, JAMA 290 (2003) 486–494, http://dx.doi.org/10.1001/jama.290.4.486.
[167] R.R. Holman, R.L. Coleman, J.C.N. Chan, et al., Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial, Lancet Diabetes Endocrinol. 5 (2017) 877–886, http://dx.doi.org/10.1016/S2213-8587(17)3030.9-1.
[168] F.A. van de Laar, P.L. Lucassen, R.P. Akkermans, et al., Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis, Diabetes Care 28 (2005) 154–163, http://dx.doi.org/10.2337/diacare.28.1.154.
[169] Novo Nordisk A/S, Victoza (liraglutide) Prescribing Information, 2019. https://www.novo-pi.com/victoza.pdf (accessed 16.08.19).
[170] Novo Nordisk A/S, Ozempic (semaglutide) Prescribing Information, 2019. Available from: https://www.novo-pi.com/ozempic.pdf.
[171] M.A. Nauck, M.L. Muus Ghorbani, E. Kreiner, et al., Effects of liraglutide compared with placebo on events of acute gallbladder or biliary disease in patients with type 2 diabetes at high risk for cardiovascular events in the LEADER randomized trial, Diabetes Care (2019), http://dx.doi.org/10.2337/dc19-0415.
[172] C.F. Murphy, C.R. Le, Can we exonerate GLP-1 receptor agonists from blame for adverse pancreatic events? Ann. Transl. Med. 6 (2018) 186, http://dx.doi.org/10.21037/atm.2018.03.06.
[173] F. Sun, S. Wu, S. Guo, et al., Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis, Diabetes Res. Clin. Pract. 110 (2015) 26–37, http://dx.doi.org/10.1016/j.diabres.2015.07.015.
[174] M. Mazidi, P. Rezaie, H.-K. Gao, A.P. Kengne, Effect of sodium-glucose cotransport-2 inhibitors on blood pressure in people with type 2 diabetes mellitus: a systematic review and meta-analysis of 43 randomized control trials with 22 528 patients, J. Am. Heart Assoc. 6 (n.d.) e004007. https://doi.org/10.1161/JAHA.116.004007.
[175] C.L. Edridge, A.J. Dunkley, D.H. Bodicoat, et al., Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: a systematic review and meta-analysis of population based studies, PLOS ONE 10 (2015) e0126427, http://dx.doi.org/10.1371/journal.pone.0126.427.
[176] H. Yki-Järvinen, A. Dressler, M. Ziemen, H.901/300s S. Group, Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group, Diabetes Care 23 (2000) 1130–1136, http://dx.doi.org/10.2337/diacare.23.8.1130.
[177] K. Hermansen, M. Davies, T. Derezinski, et al., A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with nph insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes, Diabetes Care 29 (2006) 1269–1274, http://dx.doi.org/10.2337/dc05-1365.
[178] C. Wysham, A. Bhargava, L. Chaykin, et al., Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial, JAMA 318 (2017) 45–56, http://dx.doi.org/10.1001/jama.2017.7117.
[179] M.C. Riddle, G.B. Bolli, M. Ziemen, et al., New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1), Diabetes Care 37 (2014) 2755–2762, http://dx.doi.org/10.2337/dc14-0991.
[180] V.R. Aroda, J. Rosenstock, C. Wysham, et al., Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: The LixiLan-L randomized trial, Diabetes Care 39 (2016) 1972–1980, http://dx.doi.org/10.2337/dc16-1495.
[181] L.K. Billings, A. Doshi, D. Gouet, et al., Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin; DUAL VII randomized clinical trial, Diabetes Care (2018) dc171114, http://dx.doi.org/10.2337/dc17-1114.
[182] T.M. Polasek, M.P. Doogue, T.R.J. Thynne, Metformin treatment of type 2 diabetes mellitus in pregnancy: update on safety and efficacy, Therap. Adv. Drug Saf. 9 (2018) 287–295, http://dx.doi.org/10.1177/2042098618769831.
[183] S.M. Haffner, Abdominal obesity, insulin resistance, and cardiovascular risk in pre-diabetes and type 2 diabetes, Eur. Heart J. Suppl. 8 (2006) B20–B25, http://dx.doi.org/10.1093/eurheartj/sul004.
[184] A. Baum, J. Scarpa, E. Bruzelius, et al., Targeting weight loss interventions to reduce cardiovascular complications of type 2 diabetes: a machine learning-based post-hoc analysis of heterogeneous treatment effects in the Look AHEAD trial, Lancet Diabetes Endocrinol. 5 (2017) 808–815, http://dx.doi.org/10.1016/S2213-8587(17)3017.6-6.
[185] T.I. de Vries, J.A.N. Dorresteijn, Y. van der Graaf, et al., Heterogeneity of treatment effects from an intensive lifestyle weight loss intervention on cardiovascular events in patients with type 2 diabetes: data from the look AHEAD trial, Diabetes Care 42 (2019) 1988–1994, http://dx.doi.org/10.2337/dc19-0776.
[186] F. Magkos, G. Fraterrigo, J. Yoshino, et al., Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity, Cell Metab. 23 (2016) 591–601, http://dx.doi.org/10.1016/j.cmet.2016.02.005.
[187] L.V. Gaal, A. Scheen, Weight management in type 2 diabetes: current and emerging approaches to treatment, Diabetes Care 38 (2015) 1161–1172, http://dx.doi.org/10.2337/dc14-1630.
[188] M. Corriere, N. Rooparinesingh, R.R. Kalyani, Epidemiology of diabetes and diabetes complications in the elderly: an emerging public health burden, Curr. Diab. Rep. 13 (2013), http://dx.doi.org/10.1007/s11892-013-0425-5.
[189] S. Perkisas, M. Vandewoude, Where frailty meets diabetes: frailty and diabetes, Diabetes Metab. Res. Rev. 32 (2016) 261–267, http://dx.doi.org/10.1002/dmrr.2743.
[190] American Diabetes Association, 12. Older adults: standards of medical care in diabetes—2019, Diabetes Care 42 (2019) S139–S147, http://dx.doi.org/10.2337/dc19-S012.
[191] H. Umegaki, Sarcopenia and diabetes: hyperglycemia is a risk factor for age-associated muscle mass and functional reduction, J. Diabetes Investig. 6 (2015) 623–624, http://dx.doi.org/10.1111/jdi.1236.5.
[192] V. Hainer, I. Aldhoon-Hainerová, Obesity paradox does exist, Diabetes Care 36 (2013) S276–S281, http://dx.doi.org/10.2337/dcS13-2023.
[193] M.-J. Ko, H.-C. Chiu, S.-H. Jee, et al., Postprandial blood glucose is associated with generalized pruritus in patients with type 2 diabetes, Eur. J. Dermatol. 23 (2013) 688–693, http://dx.doi.org/10.1684/ejd.2013.2100.
[194] O. Nitzan, M. Elias, B. Chazan, W. Saliba, Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management, Diabetes Metab. Syndr. Obes. 8 (2015) 129–136, http://dx.doi.org/10.2147/DMSO.S.5179.2.
[195] D. LeRoith, G.J. Biessels, S.S. Braithwaite, et al., Treatment of diabetes in older adults: an endocrine society clinical practice guideline, J. Clin. Endocrinol. Metab. 104 (2019) 1520–1574, http://dx.doi.org/10.1210/jc.2019-0019.8.
[196] A.J. Sinclair, G. Paolisso, M. Castro, et al., European diabetes working party for older people 2011 clinical guidelines for type 2 diabetes mellitus. Executive Summary, Diabetes Metab. 37 (2011) S27–S38, http://dx.doi.org/10.1016/S1262-3636(11)70962-4.

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[197] R. Ritzel, S.B. Harris, H. Baron, et al., A randomized controlled trial comparing efficacy and safety of insulin glargine 300 units/ml versus 100 units/ml in older people with type 2 diabetes: results from the SENIOR study, Diabetes Care 41 (2018) 1672–1680, http://dx.doi.org/10.2337/dc18-0168.
[198] G. Sesti, R. Antonelli Incalzi, E. Bonora, et al., Management of diabetes in older adults, Nutr. Metabol. Cardiovas. Dis. 28 (2018) 206–218, http://dx.doi.org/10.1016/j.numecd.2017.11.007.
[199] The European Definition of GP/FM | WONCA Europe, (n.d.). https://www.woncaeurope.org/gp-definitions (accessed 18.10.19).
[200] Sanofi-Aventis Canada Inc, Glucophage Product Monograph, 2018, http://products.sanofi.ca/en/glucophage.pdf (accessed 16.08.19).
[201] M.S. Fineman, L.Z. Shen, K. Taylor, et al., Effectiveness of progressive dose-escalation of exenatide(exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes, Diabetes Metab. Res. Rev. 20 (2004) 411–417, http://dx.doi.org/10.1002/dmrr.499.
[202] S. Geerlings, V. Fonseca, D. Castro-Diaz, et al., Genital and urinary tract infections in diabetes: Impact of pharmacologically-induced glucosuria, Diabetes Res. Clin. Pract. 103 (2014) 373–381, http://dx.doi.org/10.1016/j.diabres.2013.12.052.
[203] I.C. Lega, S.E. Bronskill, M.A. Campitelli, et al., Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: A population-based study of older women and men with diabetes, Diabetes Obes. Metabol. 21 (2019) 2394–2404, http://dx.doi.org/10.1111/dom.1382.0.
[204] D.S. Hsia, O. Grove, W.T. Cefalu, An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus, Curr. Opin. Endocrinol. Diabetes Obes. (2017) 1, http://dx.doi.org/10.1097/MED.0000000000000311.
[205] A. Ptaszynska, S.M. Cohen, E.M. Messing, et al., Assessing bladder cancer risk in type 2 diabetes clinical trials: the dapagliflozin drug development program as a 'case study', Diabetes Ther. 6 (2015) 357–375, http://dx.doi.org/10.1007/s13300-015-0128-9.
[206] jardiance-epar-product-information_en.pdf, (n.d.). https://www.ema.europa.eu/en/documents/product-information/jardiance-epar-product-information_en.pdf (accessed 22.04.20).
[207] Merck & Co., Inc, Januvia (sitagliptin) Prescribing Information, 2019. https://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_pi.pdf (accessed 16.08.19).
[208] Bristol-Myers Squibb Company, Onglyza (saxagliptin) Prescribing Information, 2009, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022350lbl.pdf (accessed 16.08.19).
[209] Boehringer Ingelheim Pharmaceuticals Inc, Tradjenta (linagiptin) Prescribing Information, 2019, https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Tradjenta/Tradjenta.pdf (accessed 06.08.19).
[210] D. Sola, L. Rossi, G.P.C. Schianca, et al., State of the art paper Sulfonylureas and their use in clinical practice, AOMS 4 (2015) 840–848, http://dx.doi.org/10.5114/aoms.2015.5330.4.
[211] A. Jonsson, T. Rydberg, A. Melander, G. Sterner, Pharmacokinetics of glibenclamide and its metabolites in diabetic patients with impaired renal function, Euro. J. Clin. Pharmacol. 53 (1998) 429–435, http://dx.doi.org/10.1007/s002280050403.
[212] P. Shah, S. Mudaliar, Pioglitazone: side effect and safety profile, Expert Opin. Drug Safety 9 (2010) 347–354, http://dx.doi.org/10.1517/14740331003623218.
[213] S.L. Anderson, J.C. Marrs, Antihyperglycemic medications and cardiovascular risk reduction, Eur. Endocrinol. 13 (2017) 86–90, http://dx.doi.org/10.17925/EE.201713.02.86.
[214] W.T. Cefalu, S. Kaul, H.C. Gerstein, et al., Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a diabetes care editors' expert forum, Diabetes Care 41 (2018) 14–31, http://dx.doi.org/10.2337/dci17-0057.
[215] W.B. White, C.P. Cannon, S.R. Heller, et al., Alogliptin after acute coronary syndrome in patients with type 2 diabetes, N. Engl. J. Med. 369 (2013) 1327–1335, http://dx.doi.org/10.1056/NEJMoa.1305.889.
[216] B.M. Scirica, D.L. Bhatt, E. Braunwald, et al., Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus, N. Engl. J. Med. 369 (2013) 1317–1326, http://dx.doi.org/10.1056/NEJMoa.1307.684.
[217] J. Rosenstock, M.A. Espeand, S.E. Kahn, N. Marx, B. Zinman, Cardiovascular safety and renal microvascular outcome with linagliptin in patients with T2D at high vascular risk, 2019, https://adahighlights2019.com/articles/carolina-trial/read (accessed 04.09.19).

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